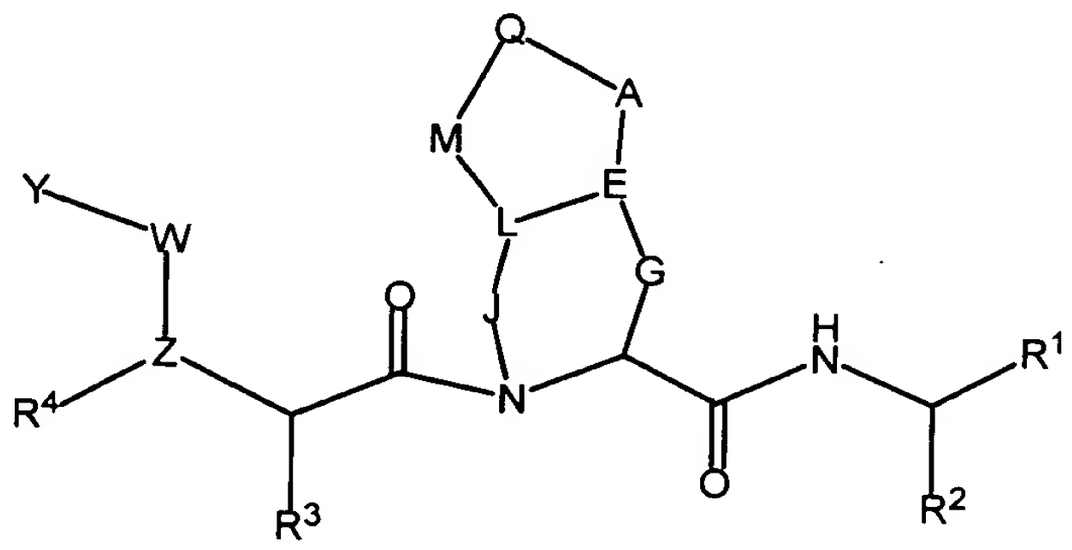
Claims

What is claimed is:

1. A compound, including enantiomers, stereoisomers, rotamers, tautomers, racemates and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound having the general structure shown in Formula I:



Formula I

wherein:

Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, , alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X^{11} or X^{12};

X^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X^{11} may be additionally optionally substituted with X^{12};

X^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido,

arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from X^{12};

R^1 is COR^5 or $B(OR)_2$, wherein R^5 is H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, or COR^7 wherein R^7 is H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10}, wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pCOR^{11}$, $[CH(R^{1'})]_pCH(OH)R^{11}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$ and $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is selected from O, N, CH or CR;

W maybe present or absent, and if W is present, W is selected from C=O, C=S, C(=N-CN), or SO_2;

Q maybe present or absent, and when Q is present, Q is CH, N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, or SO_2; and when Q is absent, M may be present or absent; when Q and M are absent, A is directly linked to L;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_2 or a bond;

E is CH, N, CR, or a double bond towards A, L or G;

G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$; and when G is absent, J is present and E is directly connected to the carbon atom in Formula I as G is linked to;

J maybe present or absent, and when J is present, J is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$, SO_2, NH, NR or O; and when J is absent, G is present and E is directly linked to N shown in Formula I as linked to J;

L may be present or absent, and when L is present, L is CH, CR, O, S or NR; and when L is absent, then M may be present or absent; and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, NR, S, SO_2, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

p is a number from 0 to 6; and

R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

wherein said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally and chemically-suitably substituted, with said term "substituted" referring to optional and chemically-suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamido, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate;

further wherein said unit N-C-G-E-L-J-N represents a five-membered or six-membered cyclic ring structure with the proviso that when said unit N-C-G-E-L-J-N represents a five-membered cyclic ring structure, or when the bicyclic ring structure in Formula I comprising N, C, G, E, L, J, N, A, Q, and M represents a five-membered cyclic ring structure, then said five-membered cyclic ring structure lacks a carbonyl group as part of the cyclic ring.

2. The compound of claim 1, wherein R^1 is COR^5, and R^5 is H, OH, $COOR^8$, $CONR^9R^{10}$.

3. The compound of claim 2, wherein R^1 is $COCONR^9R^{10}$, and R^9 is H, R^{10} is H, R^{14}, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pSO_2N\ R^{12}R^{13}$, $[CH(R^{1'})]_pCOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaralkyl.

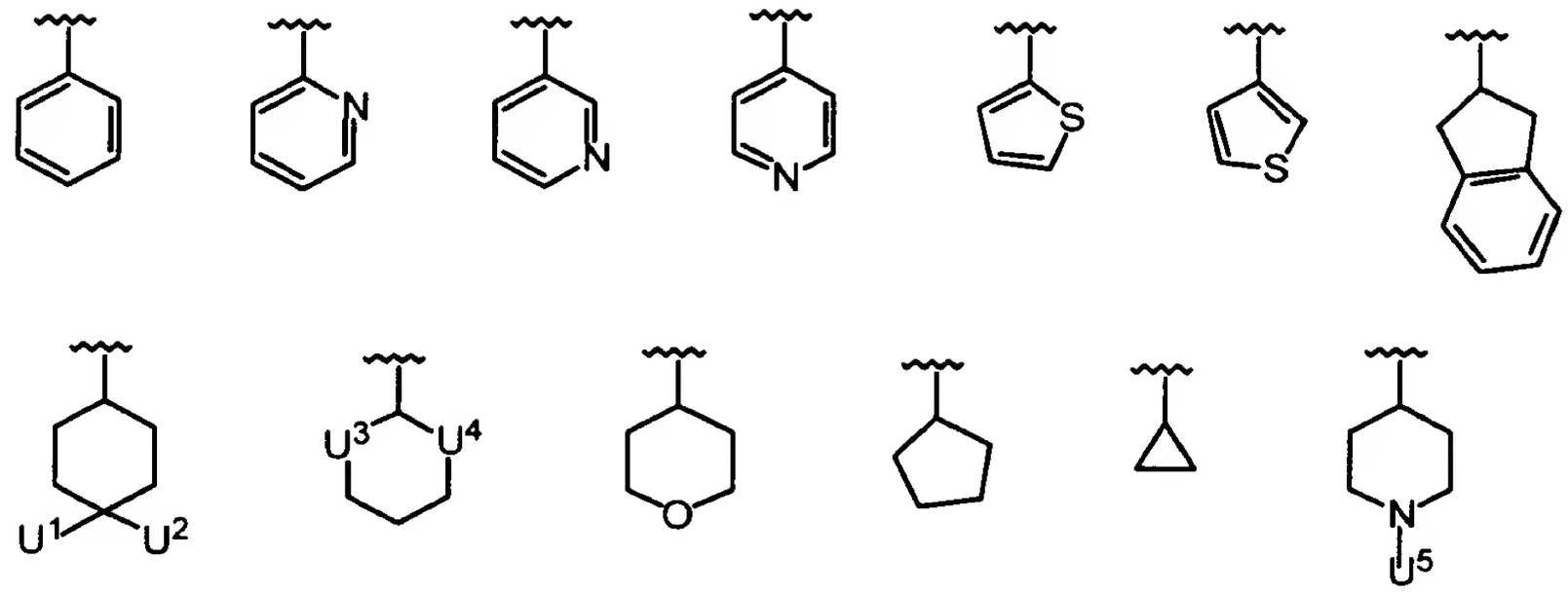
4. The compound of claim 3, wherein R^{10} is H, R^{14}, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})SO_2R^{11}$, $CH(R^{1'})CH(R^{1'})SO_2N\ R^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})COR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein $R^{1'}$ is H or alkyl, and $R^{2'}$ is phenyl, substituted phenyl, hetero atom-substituted phenyl, thiophenyl, cycloalkyl, piperidyl or pyridyl.

5. The compound of claim 4, wherein $R^{1'}$ is H.

6. The compound of claim 5, wherein R^{11} is H, methyl, ethyl, allyl, *tert*-butyl, benzyl, α-methylbenzyl, α,α-dimethylbenzyl, 1-methylcyclopropyl or 1-methylcyclopentyl;

R' is hydroxymethyl or $CH_2CONR^{12}R^{13}$;

$R^{2'}$ is independently selected from the group consisting of:



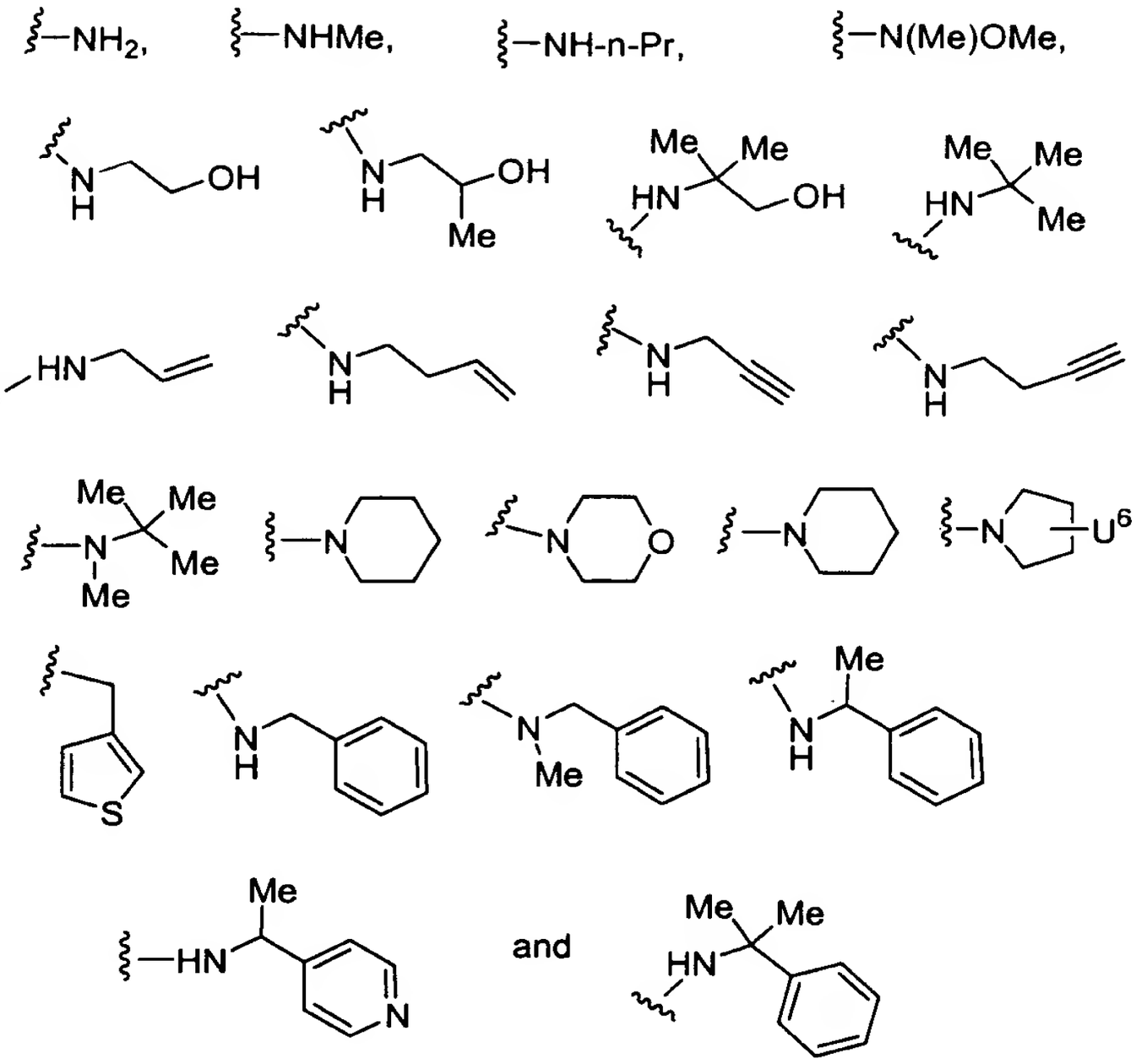
wherein:

U^1 and U^2 maybe same or different and are selected from H, F, CH_2COOH, CH_2COOMe, CH_2CONH_2, $CH_2CONHMe$, CH_2CONMe_2, azido, amino, hydroxyl, substituted amino, substituted hydroxyl;

U^3 and U^4 maybe same or different and are selected from O and S;

U^5 is selected from the moieties consisting of alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof;

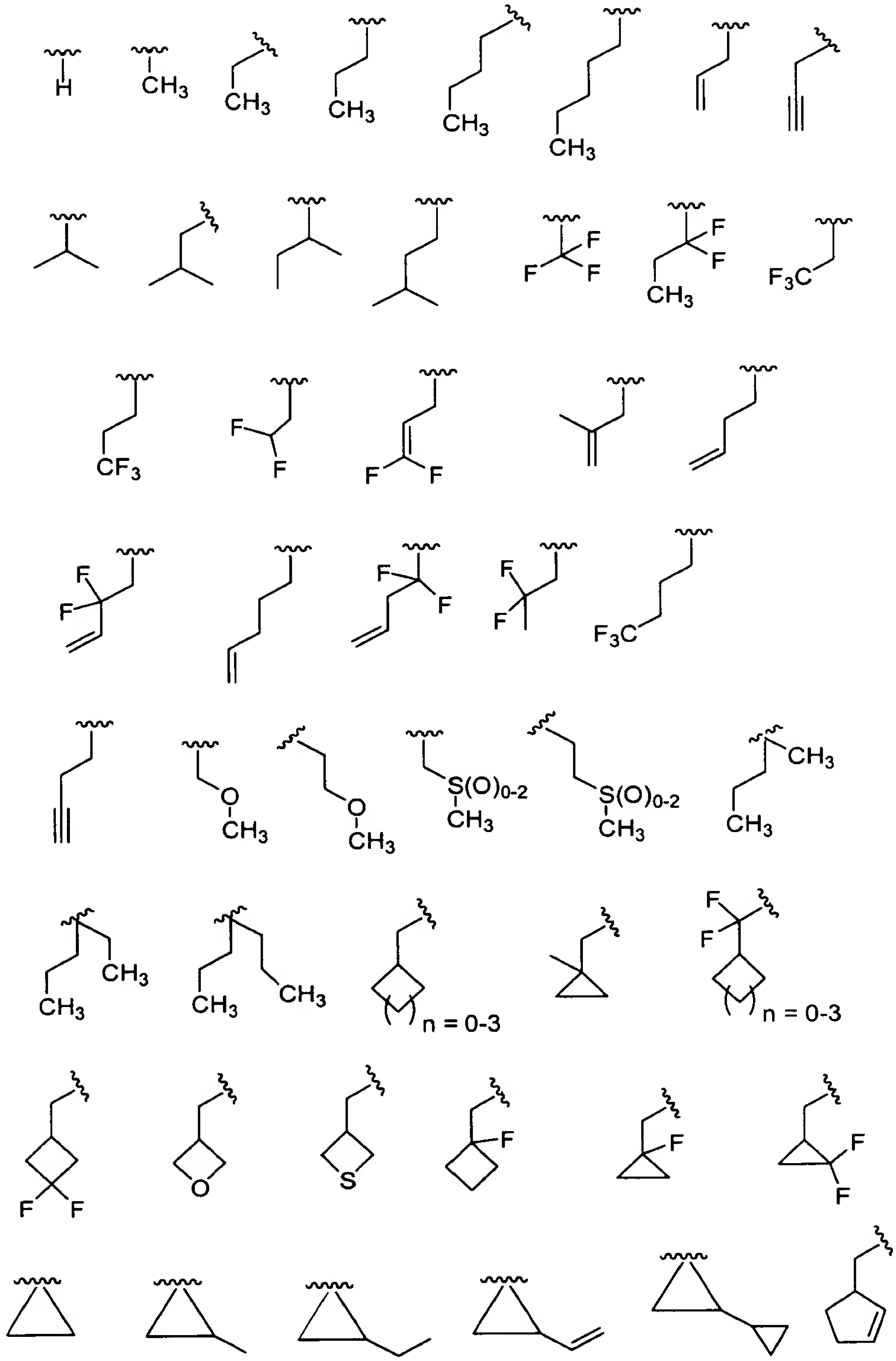
and $NR^{12}R^{13}$ is selected from the group consisting of:



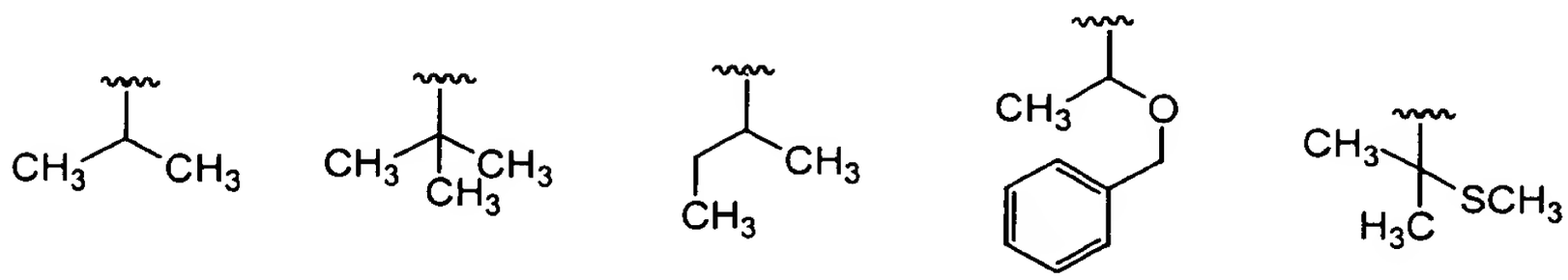
wherein U^6 is H, OH, or CH_2OH, and

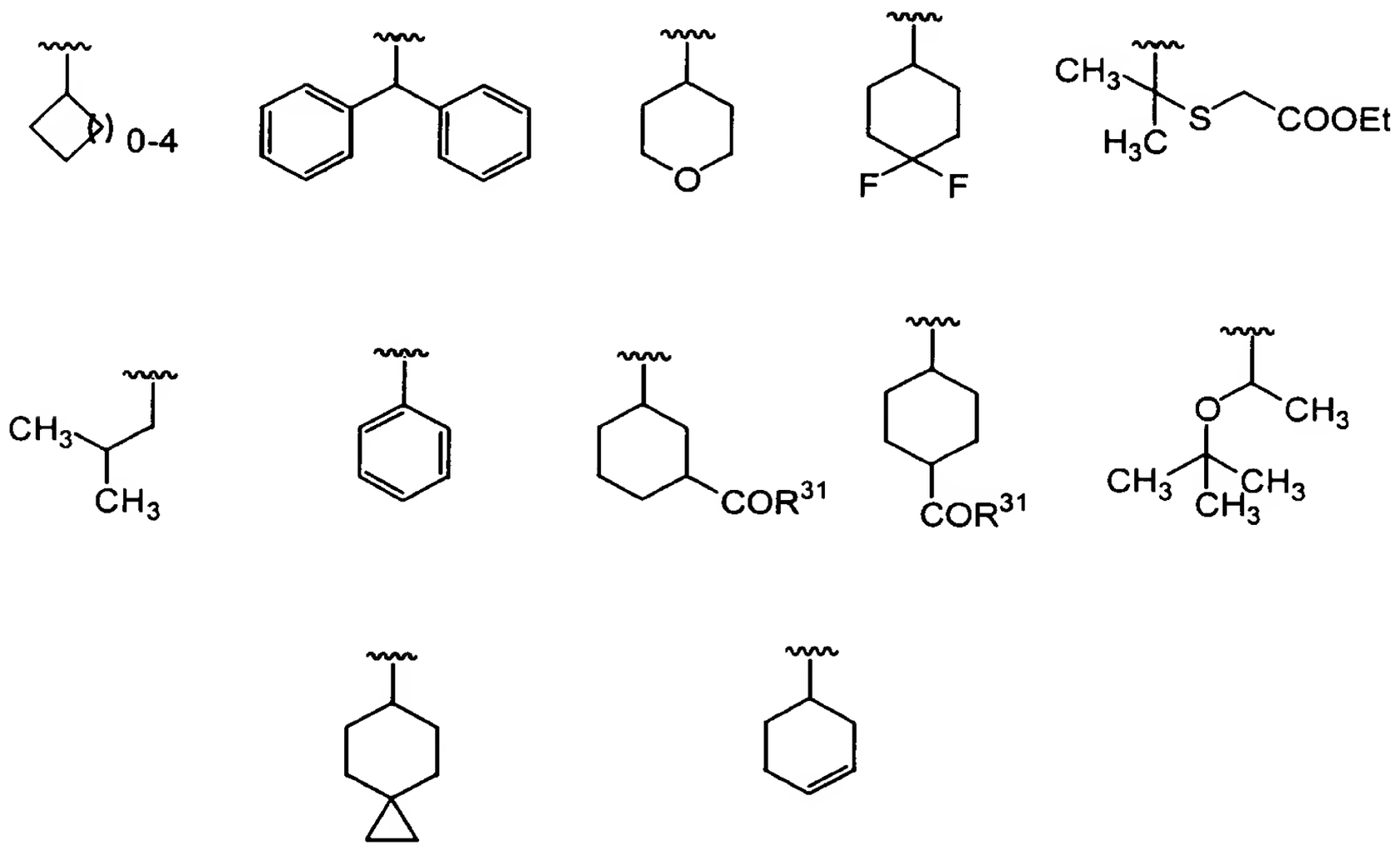
R^{14} is selected from the group consisting of: H, Me, Et, *n*-propyl, methoxy, cyclopropyl, *n*-butyl, 1-but-3-ynyl, benzyl, α-methylbenzyl, phenethyl, allyl, 1-but-3-enyl, OMe, cyclopropylmethyl.

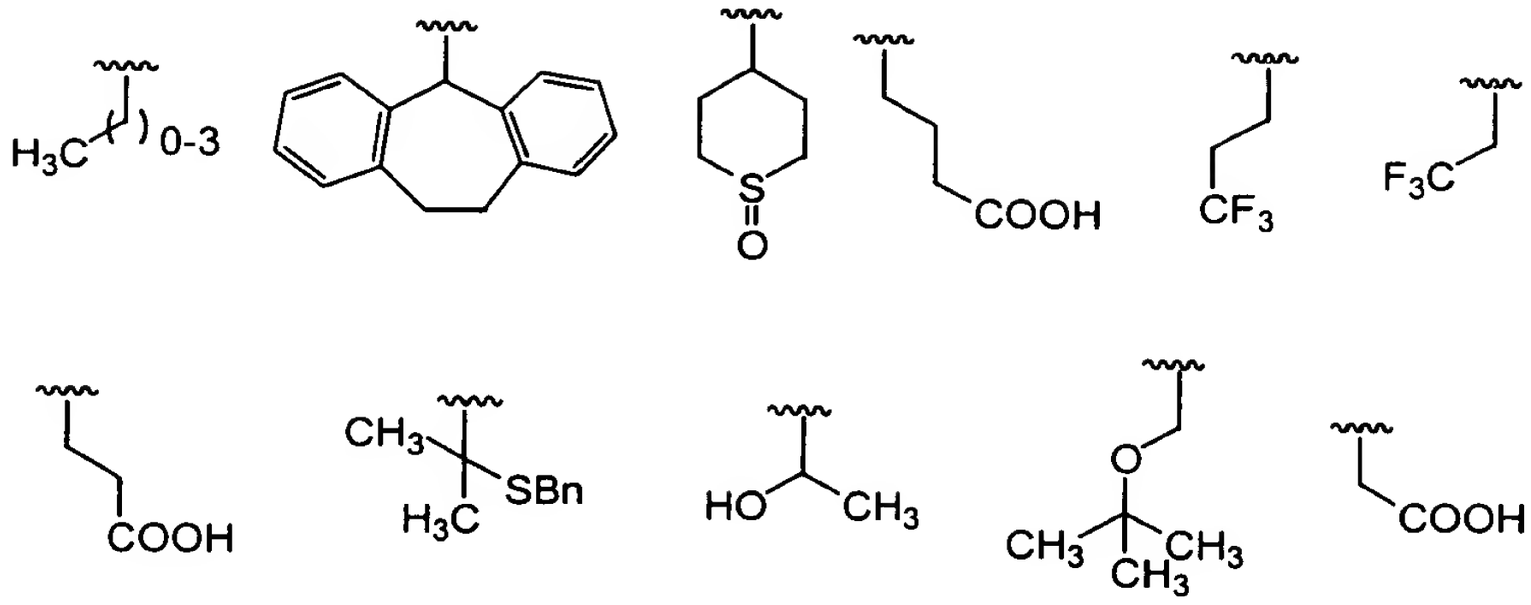
7. The compound of claim 2, wherein R^2 is selected from the group consisting of the following moieties:

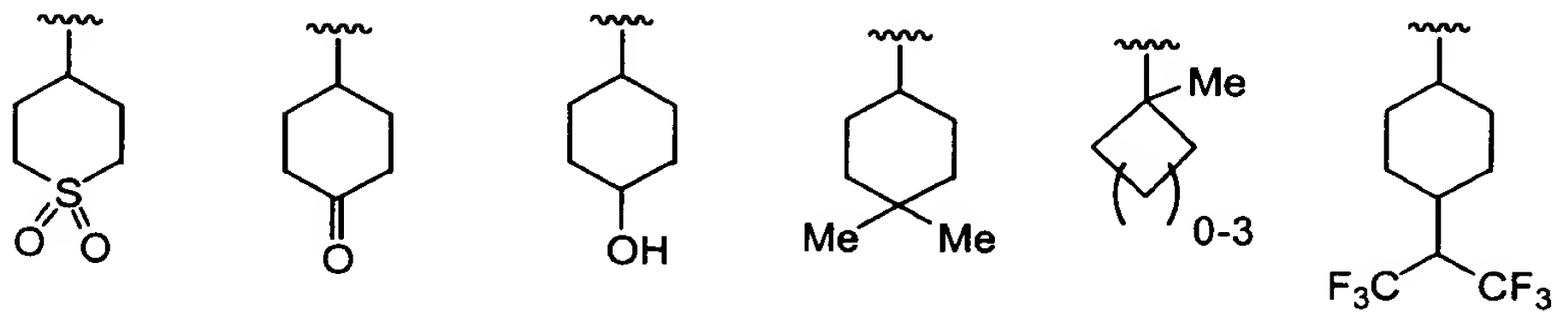


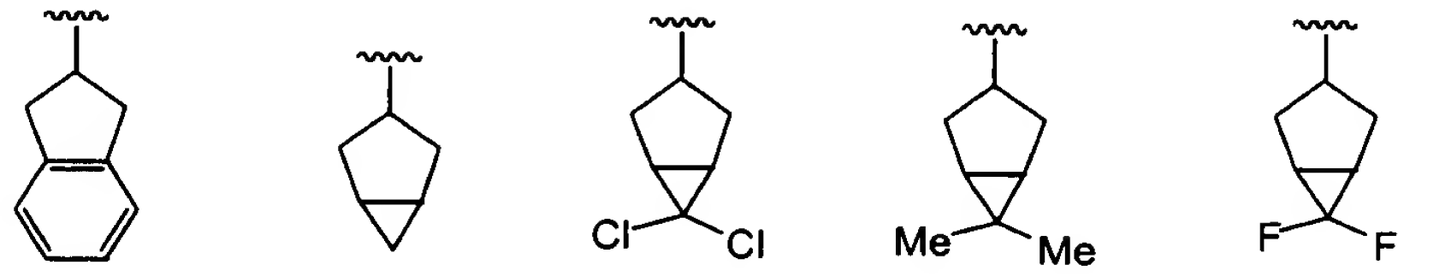
8. The compound of claim 7, wherein R^3 is selected from the group consisting of:

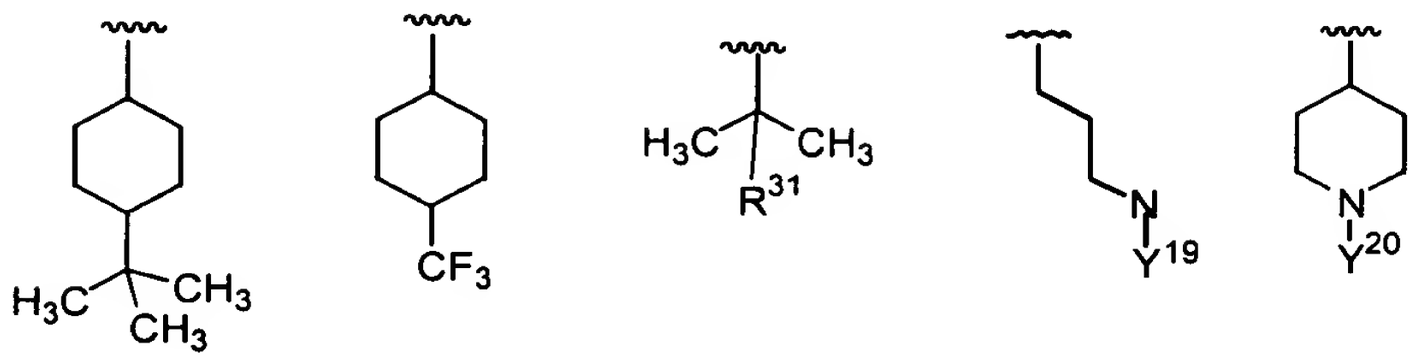








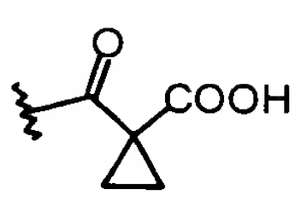
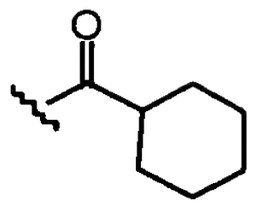
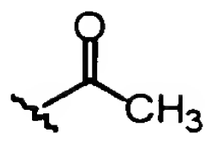
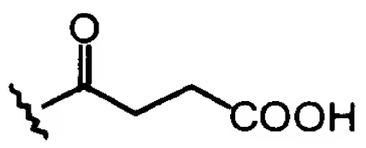
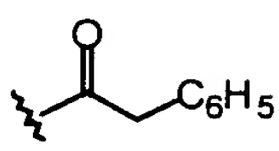
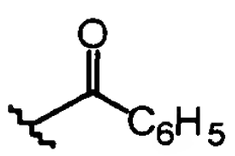




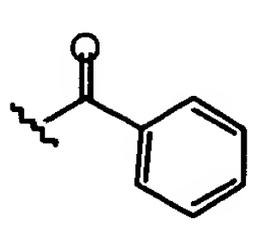
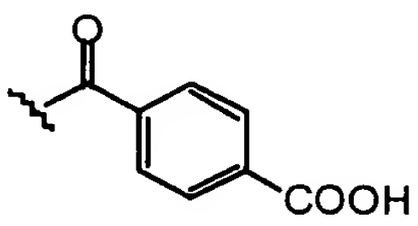
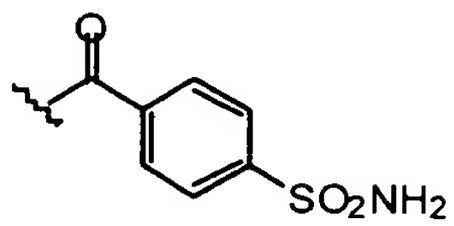
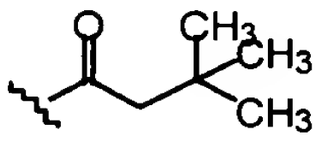
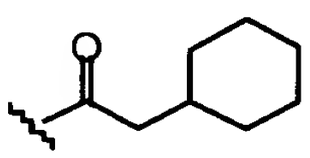
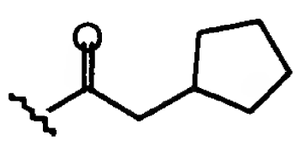
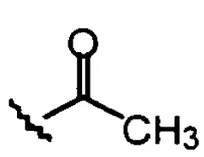
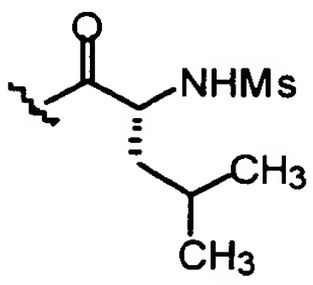
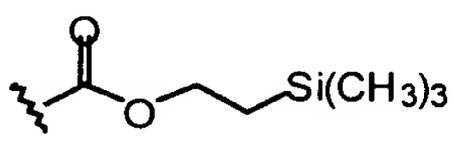
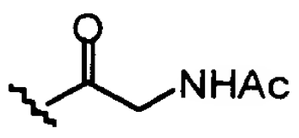
5

wherein R^{31} = OH or O-alkyl;

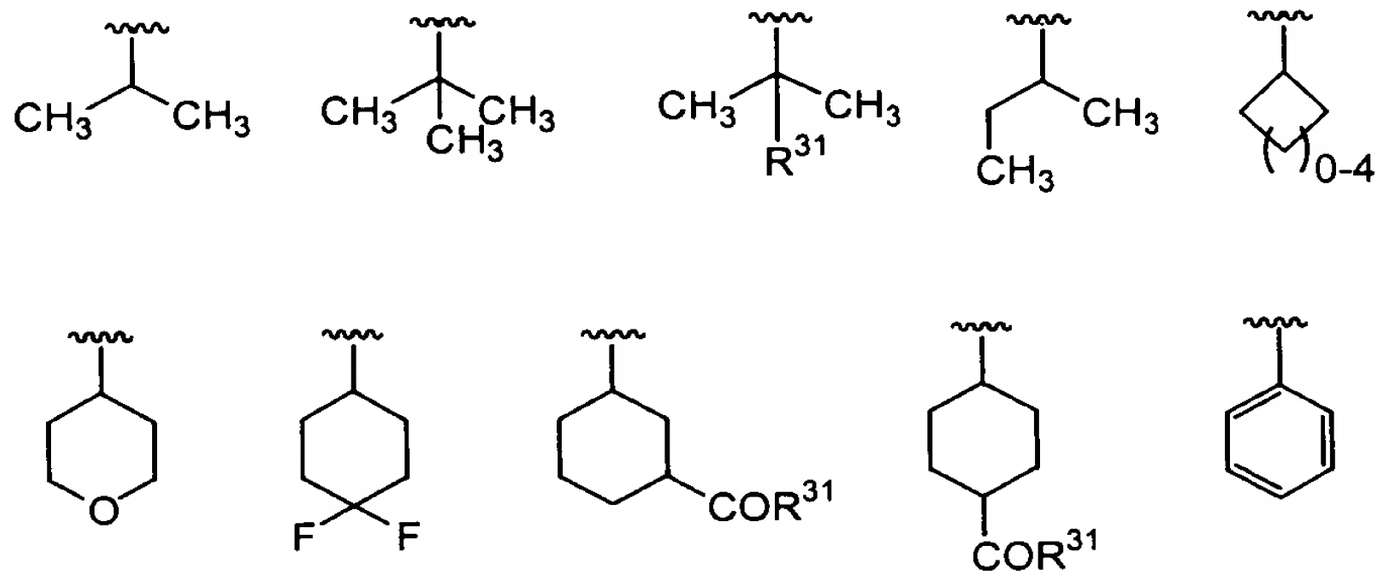
Y^{19} is selected from the following moieties:

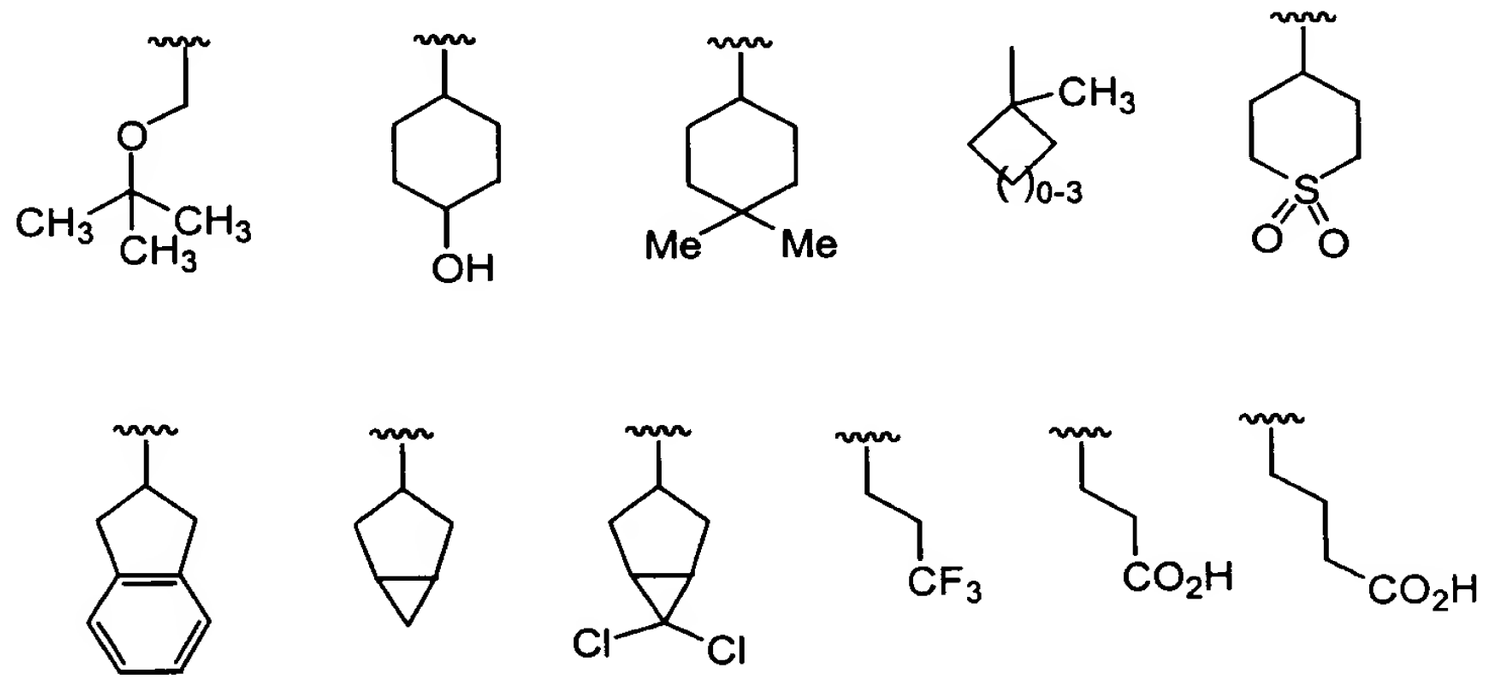







and Y^{20} is selected from the following moieties:

9. The compound of claim 8, wherein R^3 is selected from the group consisting of the following moieties:

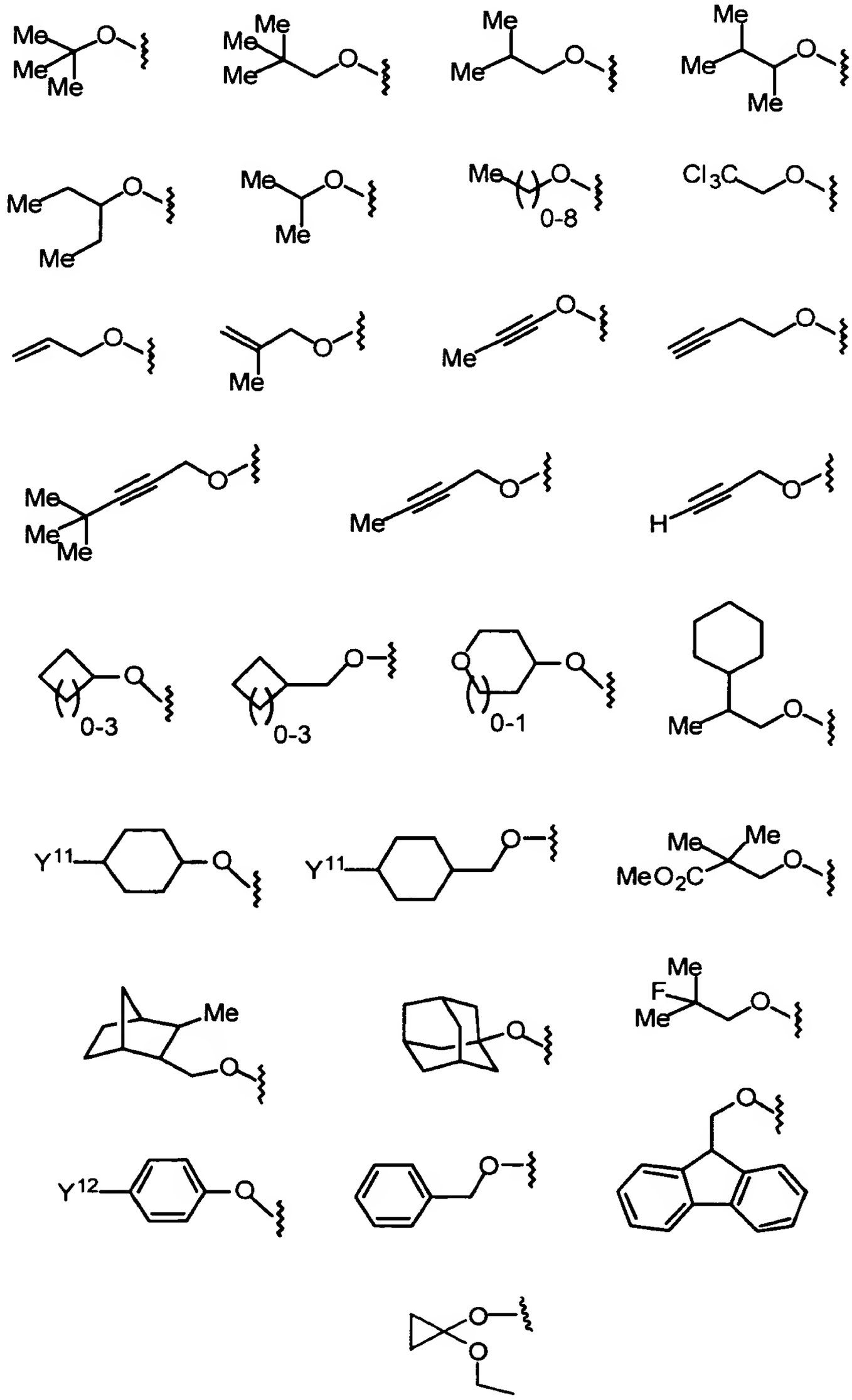


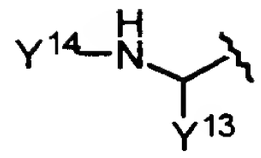


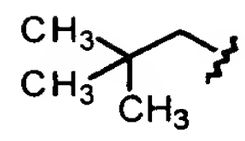
10. The compound of claim 9, wherein Z is N and R^4 is H.

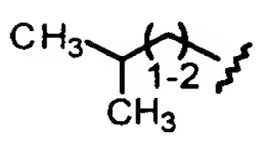
11. The compound of claim 10, wherein W is C=O.

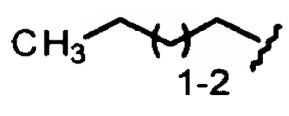
12. The compound of claim 11, wherein Y is selected from the following moieties:

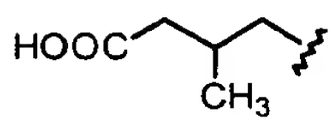


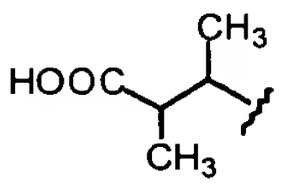


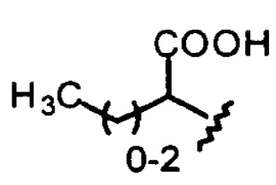


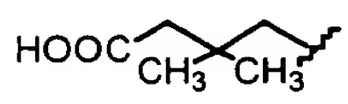


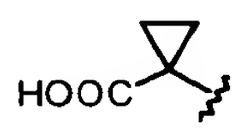


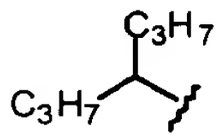


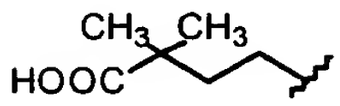


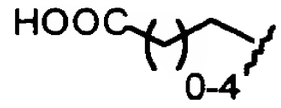


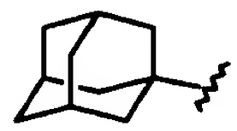


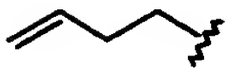


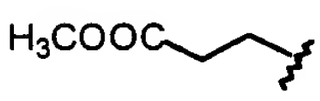


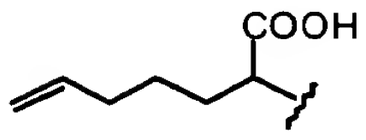


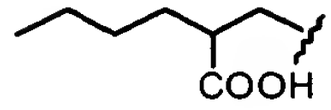


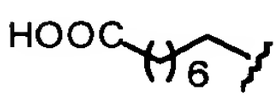


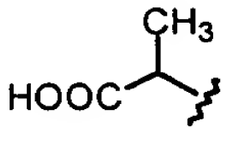


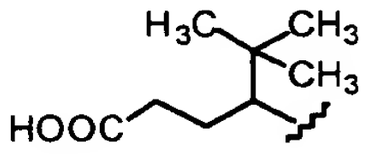


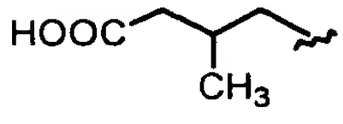


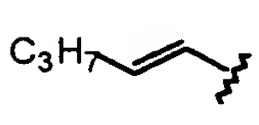


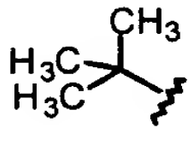


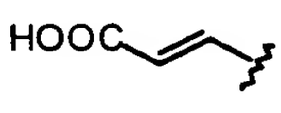


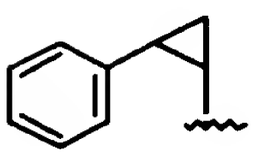


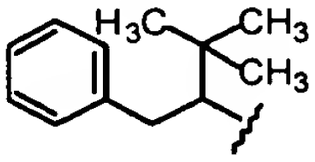


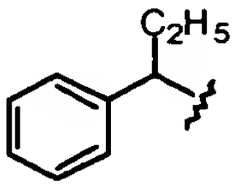


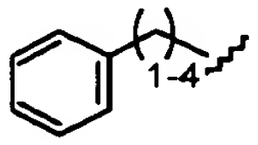


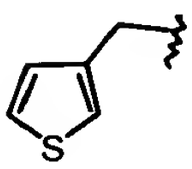


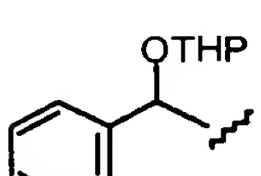


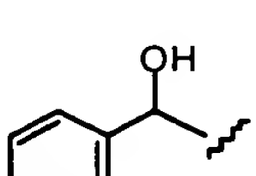


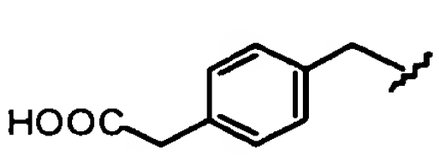


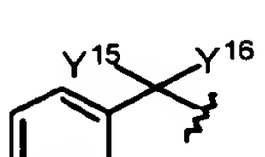












Y14
H
N
Y13

CH3
CH3
CH3

CH3
1-2
CH3

CH3
1-2

HOOC
CH3

CH3
HOOC
CH3

COOH
H3C
0-2

HOOC
CH3
CH3

HOOC

C3H7
C3H7

CH3
CH3
HOOC

HOOC
0-4

H3COOC

COOH

COOH

HOOC
6

CH3
HOOC

H3C
CH3
CH3
HOOC

HOOC
CH3

C3H7

CH3
H3C
H3C

HOOC

CH3
0-2

HOOC

COOH

H3C
CH3
CH3

C2H5

1-4

S

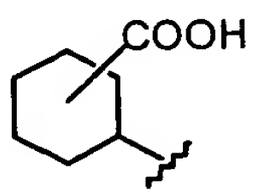
OTHP

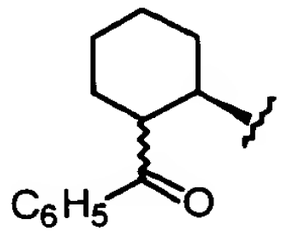
OH

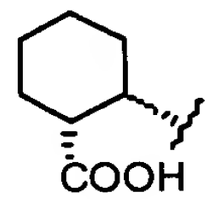
HOOC

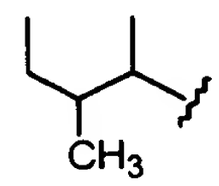
Y15
Y16

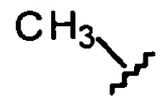

1-3

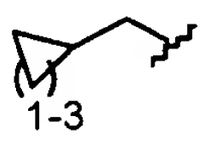

COOH

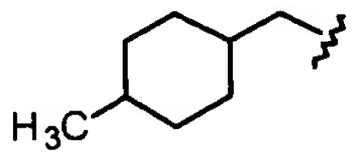

C6H5
O

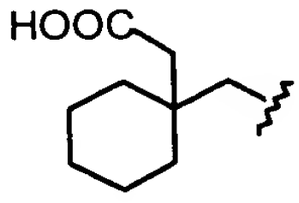

COOH

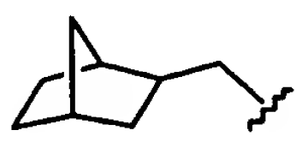

CH3

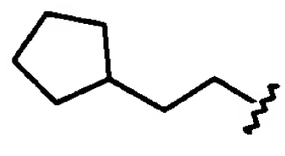

CH3

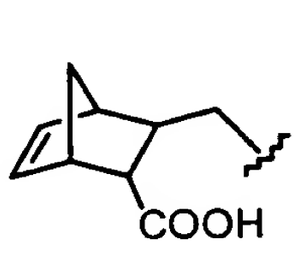

1-3

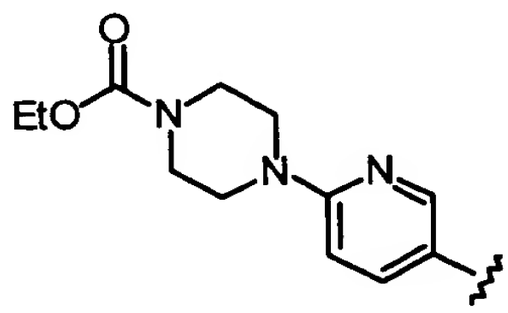

H3C

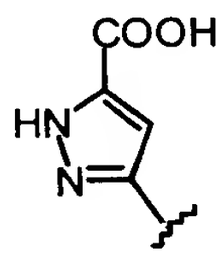

HOOC

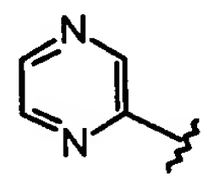


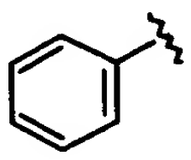


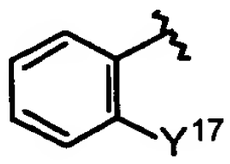

COOH

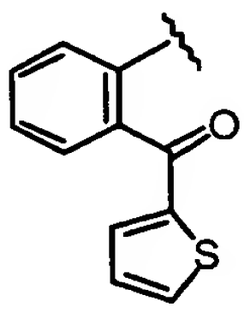

EtO
O
N
N
N

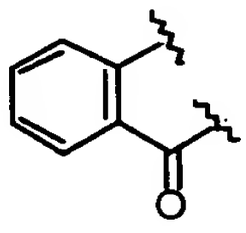

COOH
HN
N

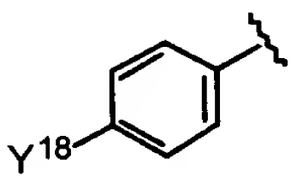

N
N

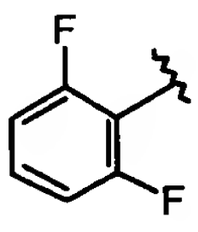


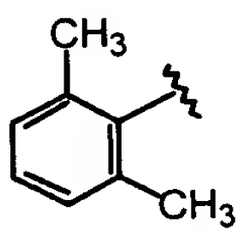

Y17

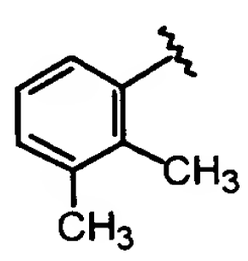

O
S

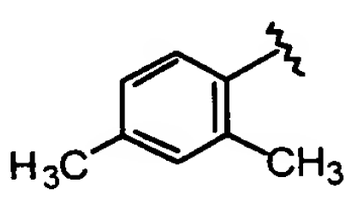

O

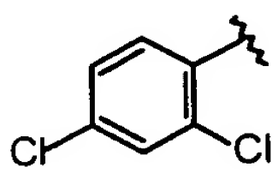

Y18

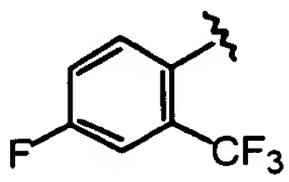

F
F

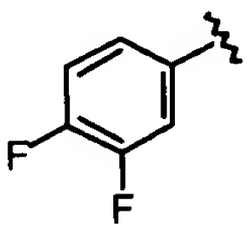

CH3
CH3

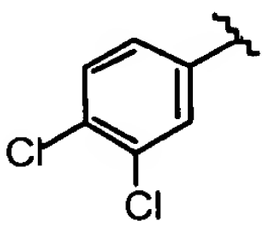

CH3
CH3

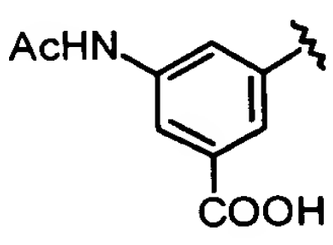

H3C
CH3

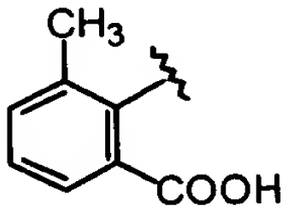

Cl
Cl

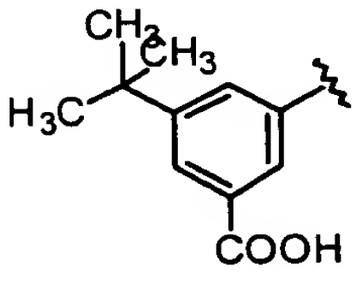

F
CF3

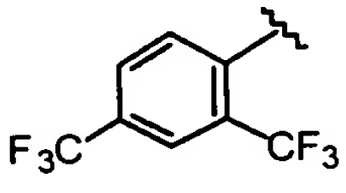

F
F

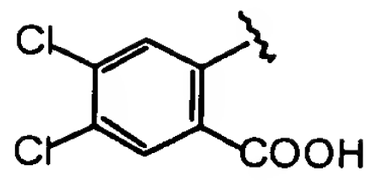
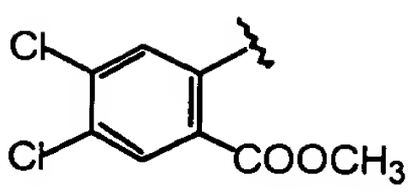
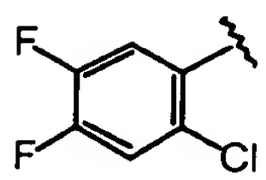
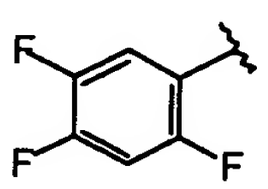
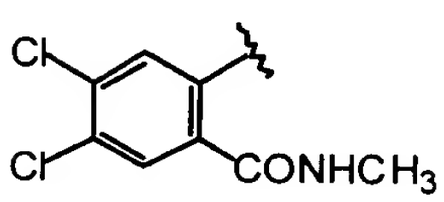
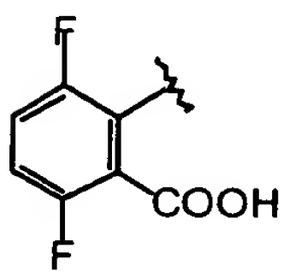
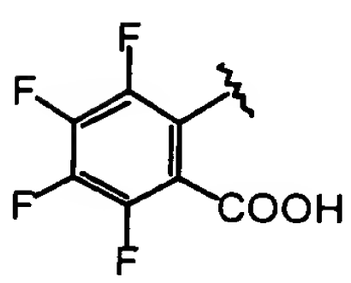
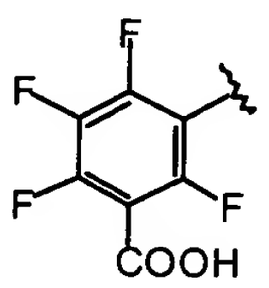
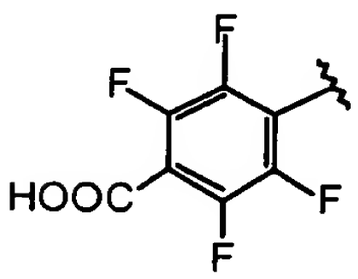
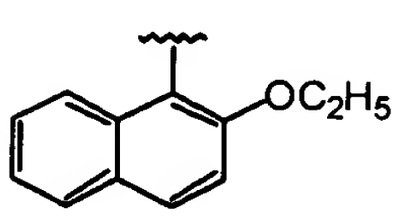
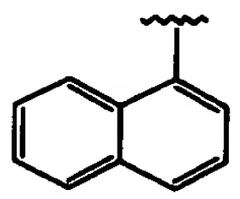
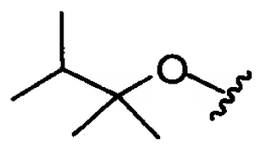
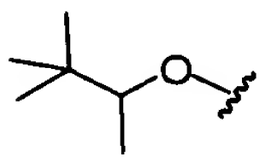
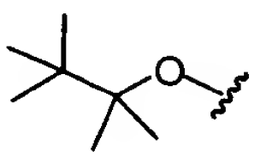
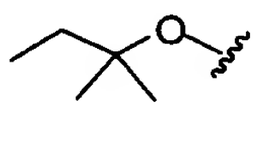
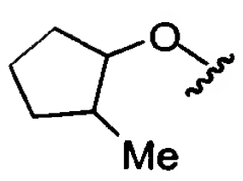
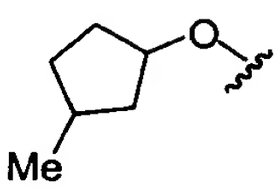
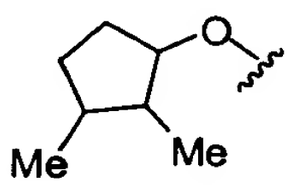
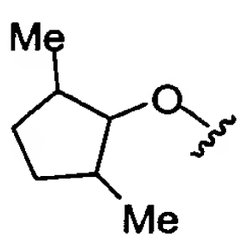
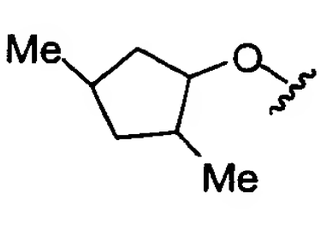
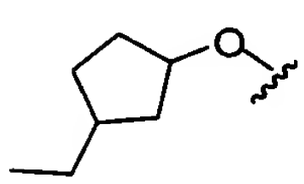
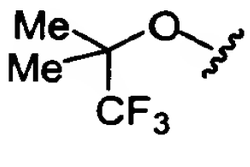
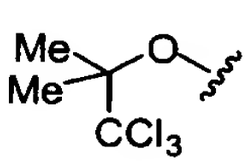
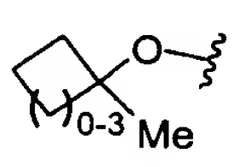
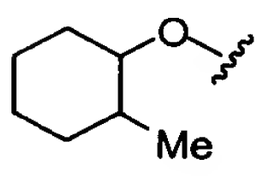
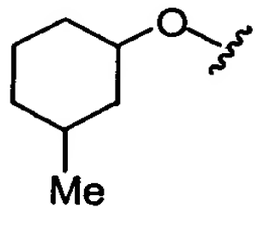
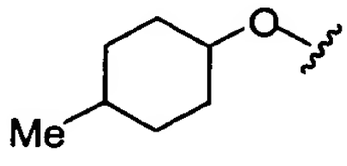
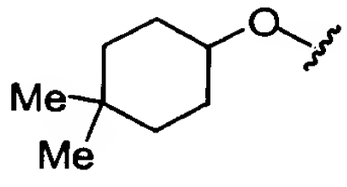
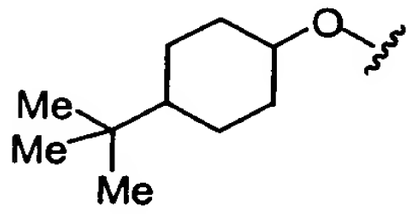
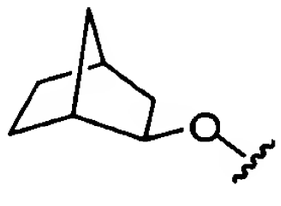
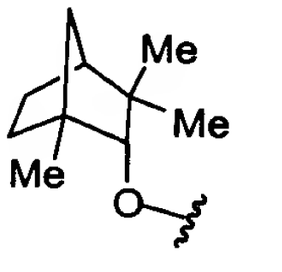
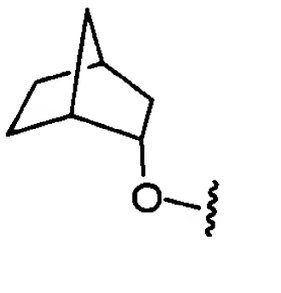

Cl
Cl

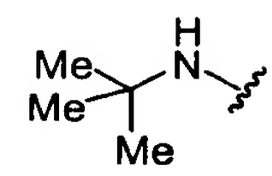

AcHN
COOH

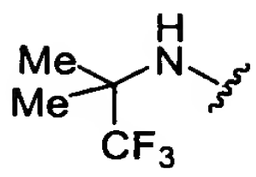

CH3
COOH

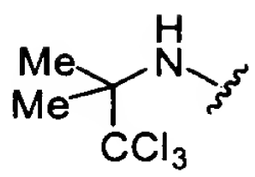

CH3
CH3
H3C
COOH

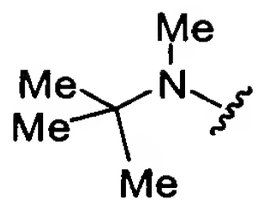

F3C
CF3

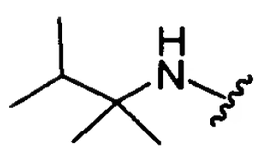

































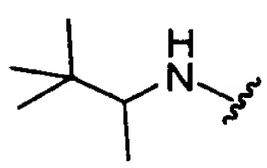


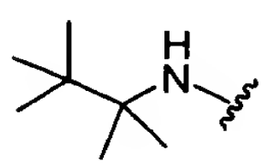


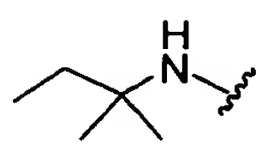


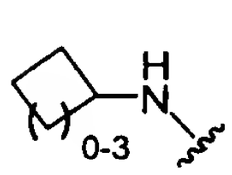


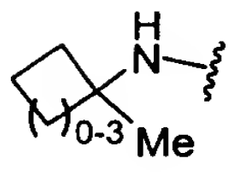


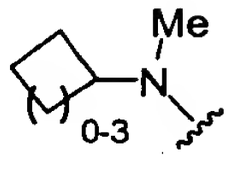


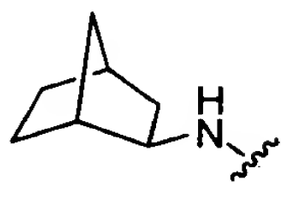


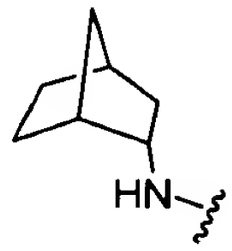


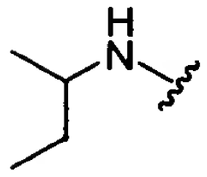


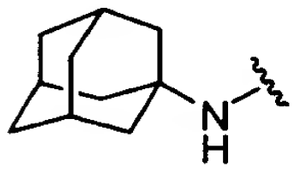


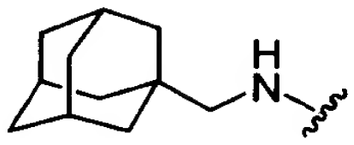


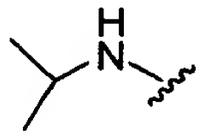










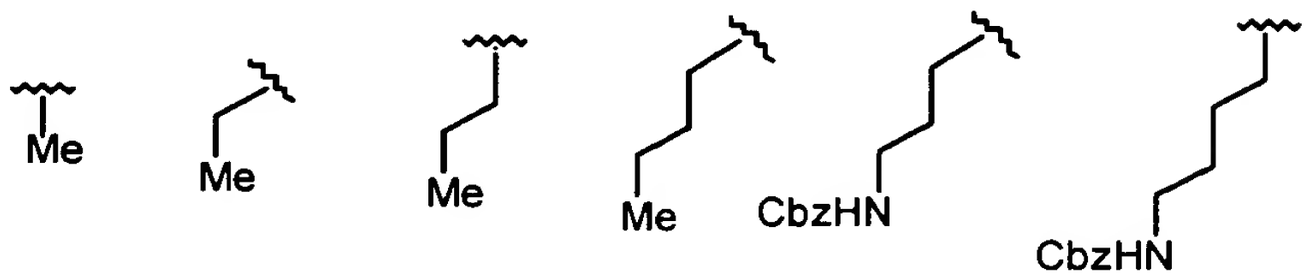


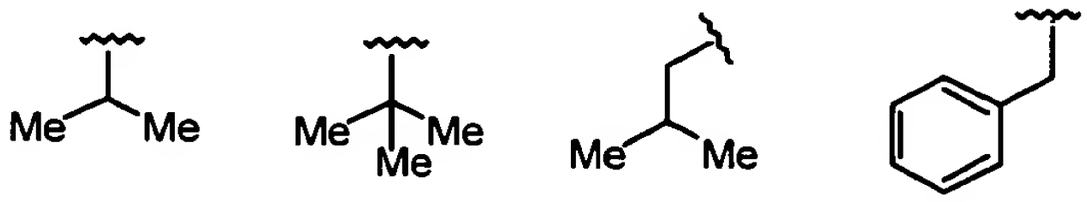
wherein:

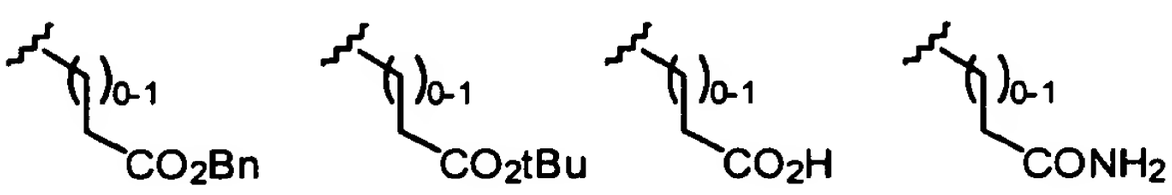
Y^{11} is selected from H, COOH, COOEt, OMe, Ph, OPh, NHMe, NHAc, NHPh, $CH(Me)_2$, 1-triazolyl, 1-imidazolyl, and $NHCH_2COOH$;

Y^{12} is selected from H, COOH, COOMe, OMe, F, Cl, or Br;

Y^{13} is selected from the following moieties:







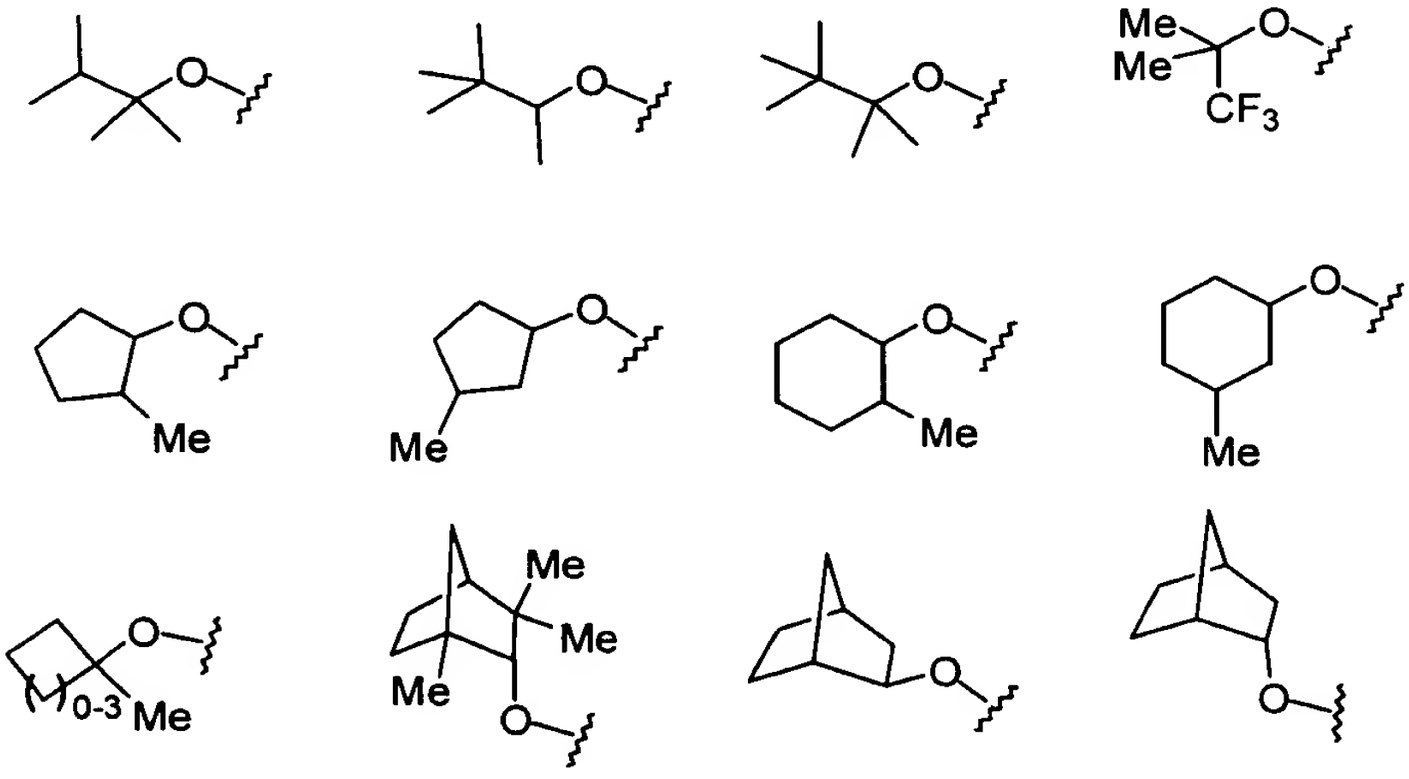
Y^{14} is selected from $MeSO_2$, Ac, Boc, iBoc, Cbz, or Alloc;

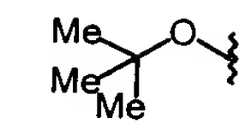
Y^{15} and Y^{16} are independently selected from alkyl, aryl, heteroalkyl, and heteroaryl;

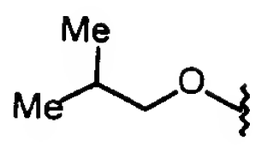
Y^{17} is CF_3, NO_2, $CONH_2$, OH, $COOCH_3$, OCH_3, OC_6H_5, C_6H_5, COC_6H_5, NH_2, or COOH; and

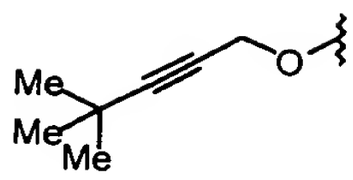
Y^{18} is $COOCH_3$, NO_2, $N(CH_3)_2$, F, OCH_3, CH_2COOH, COOH, SO_2NH_2, or $NHCOCH_3$.

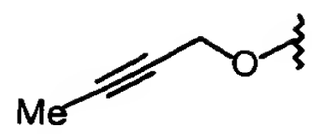
13. The compound of claim 12, wherein Y is selected from the group consisting of:

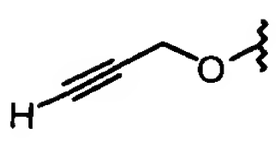


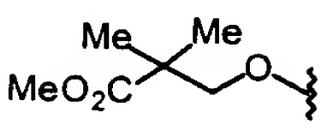


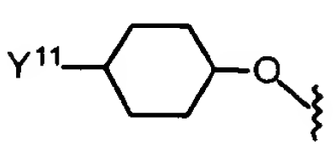


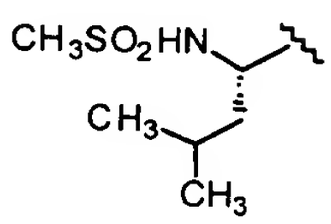


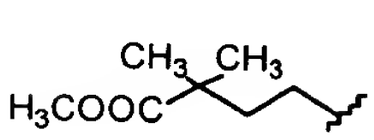


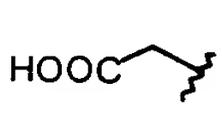


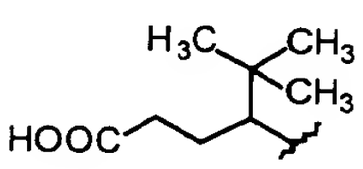


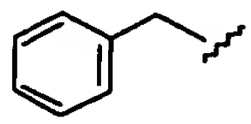


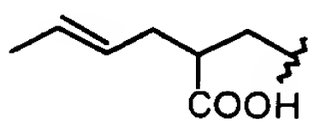


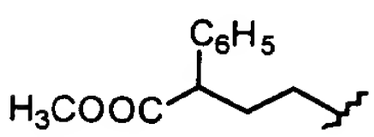


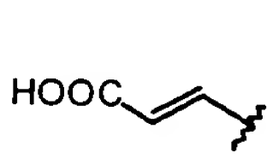


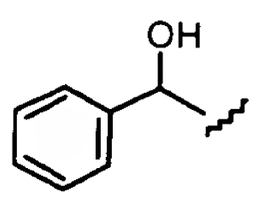


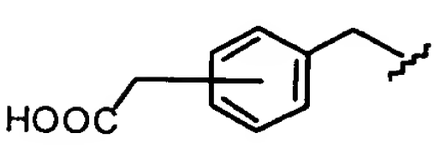


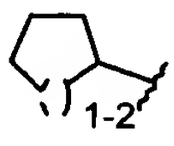


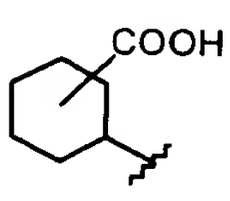


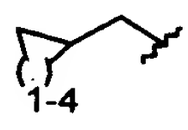


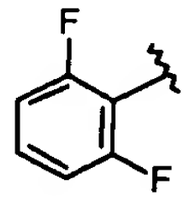


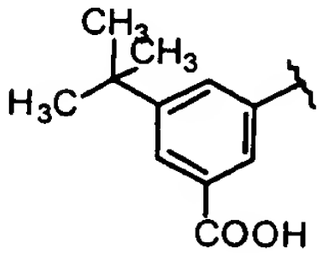


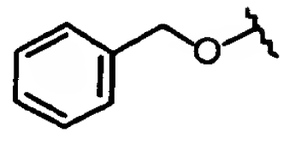


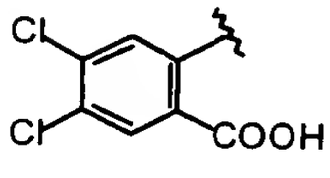


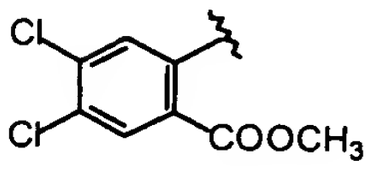


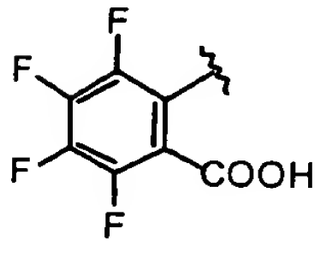


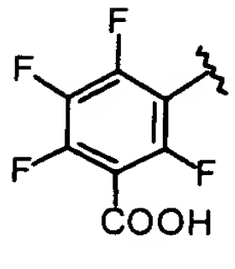


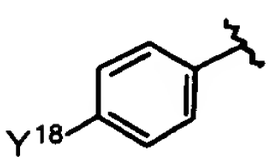


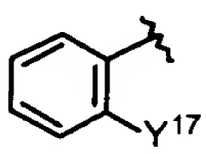


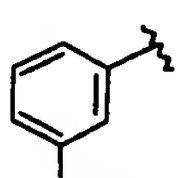


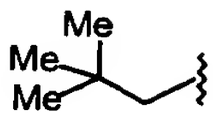


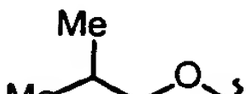


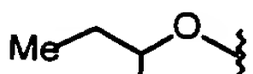


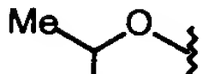










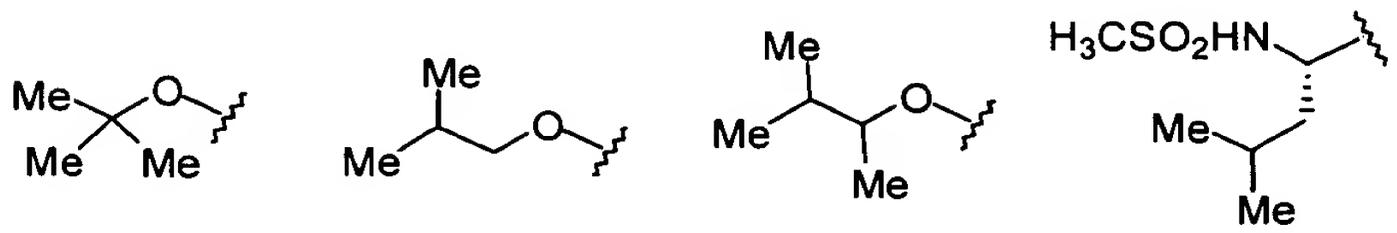
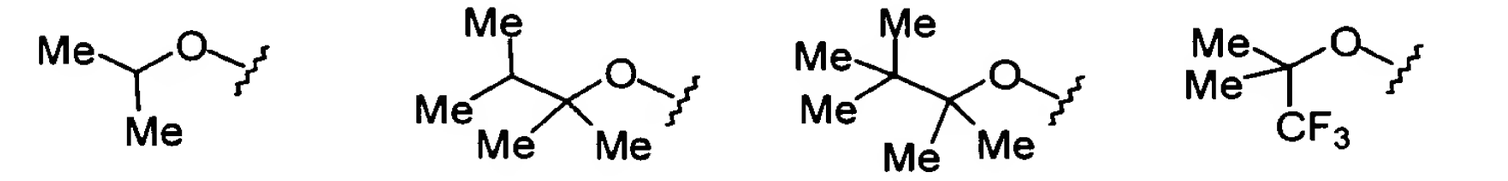
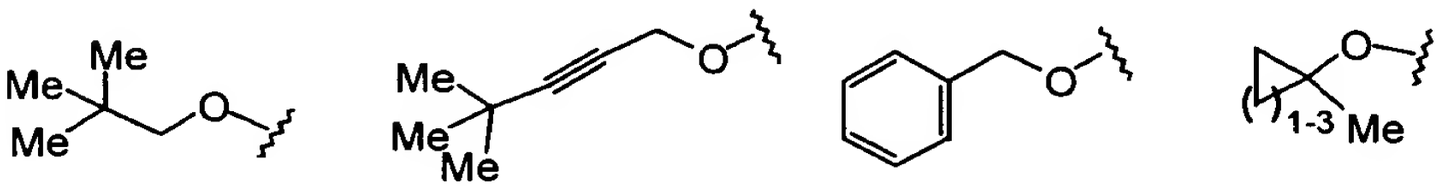
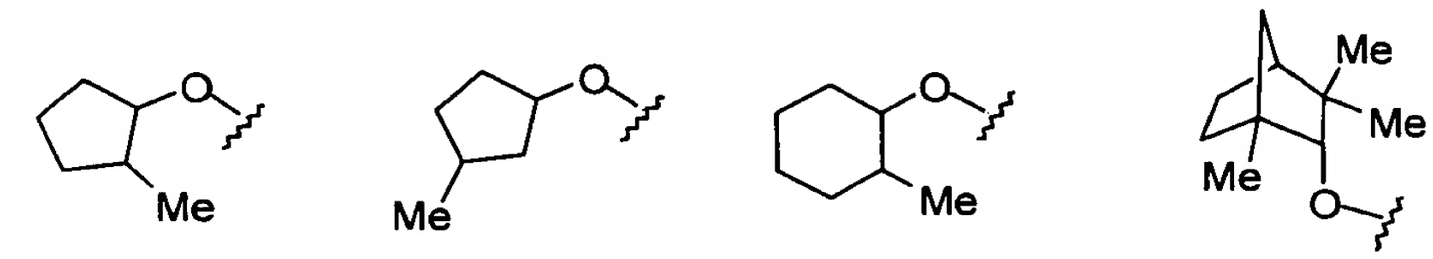
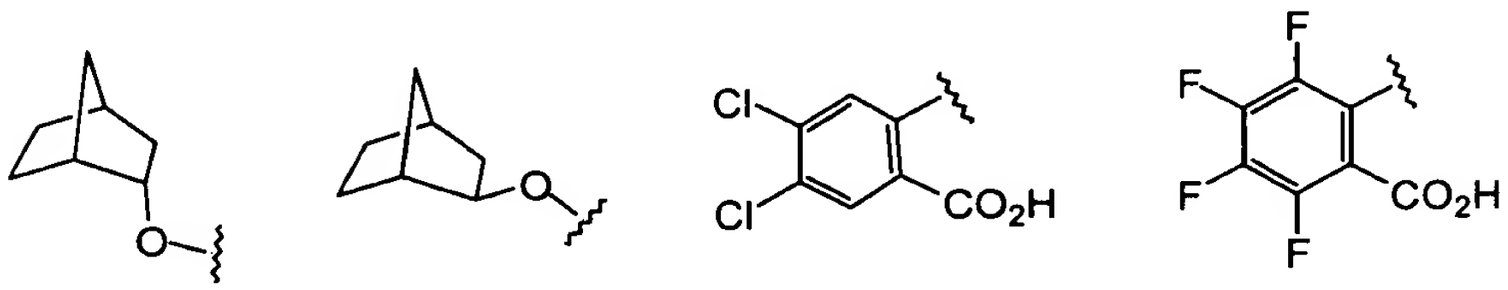
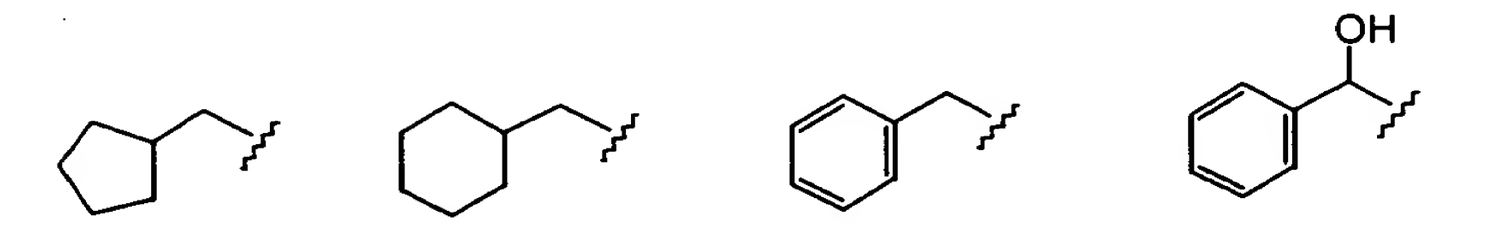
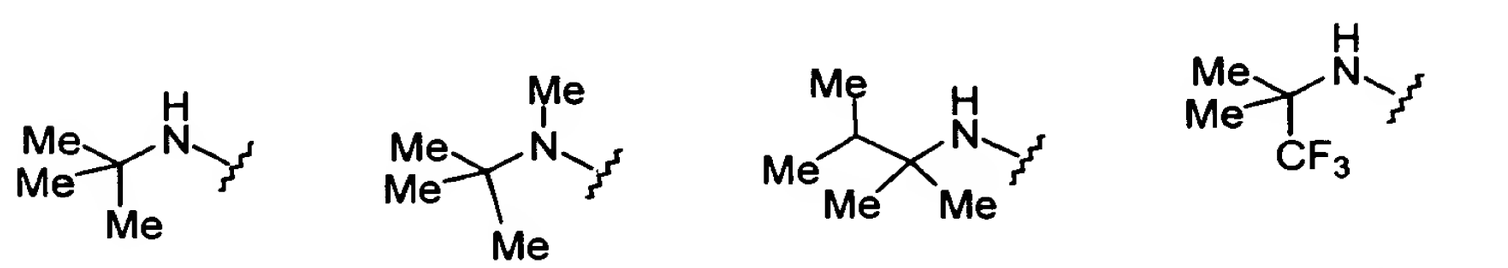
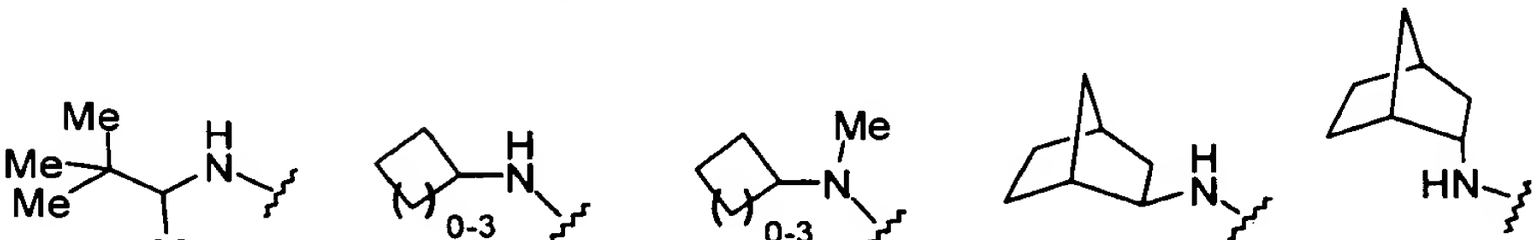
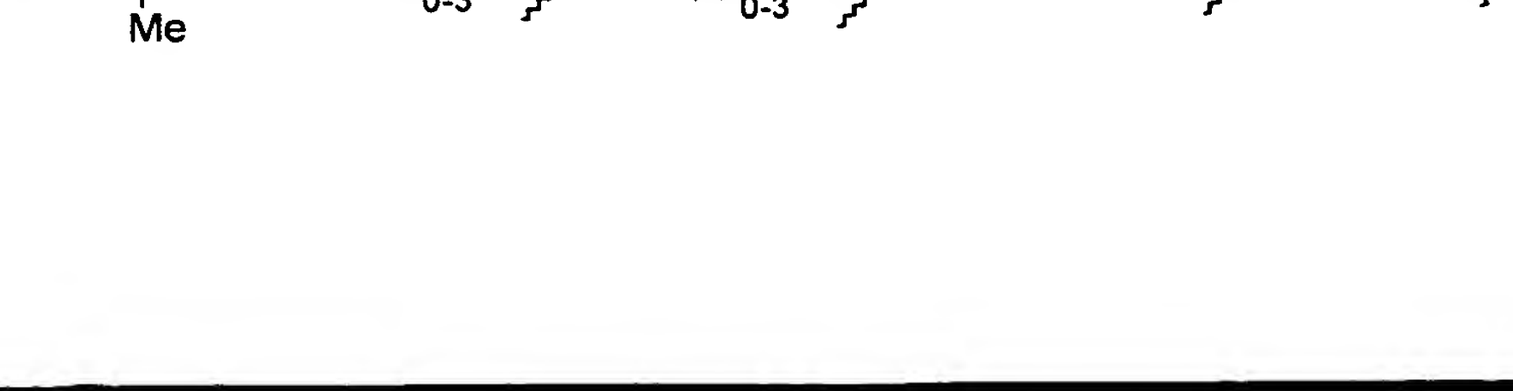


wherein:

Y^{17} = CF_3, NO_2, $CONH_2$, OH, NH_2, or COOH;

Y^{18}= F, COOH,

14. The compound of claim 13, wherein Y is selected from the group consisting of:

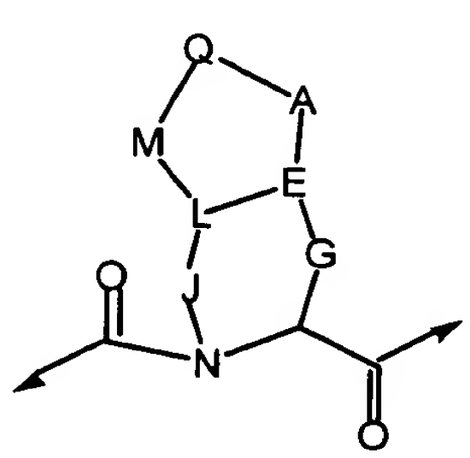










15. The compound of claim 14, wherein L and M are absent, and J is directly linked to E.

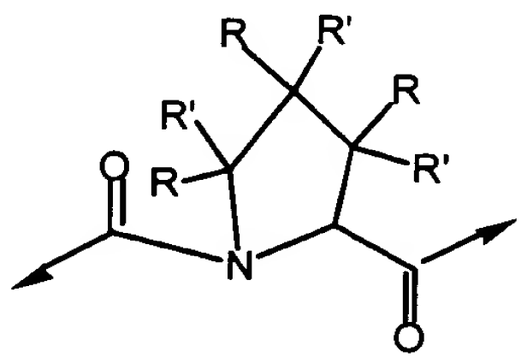
16. The compound of claim 14, wherein L, J and M are absent and E is directly linked to N.

17. The compound of claim 14, wherein G and M are absent.

18. The compound of claim 14, wherein the moiety:

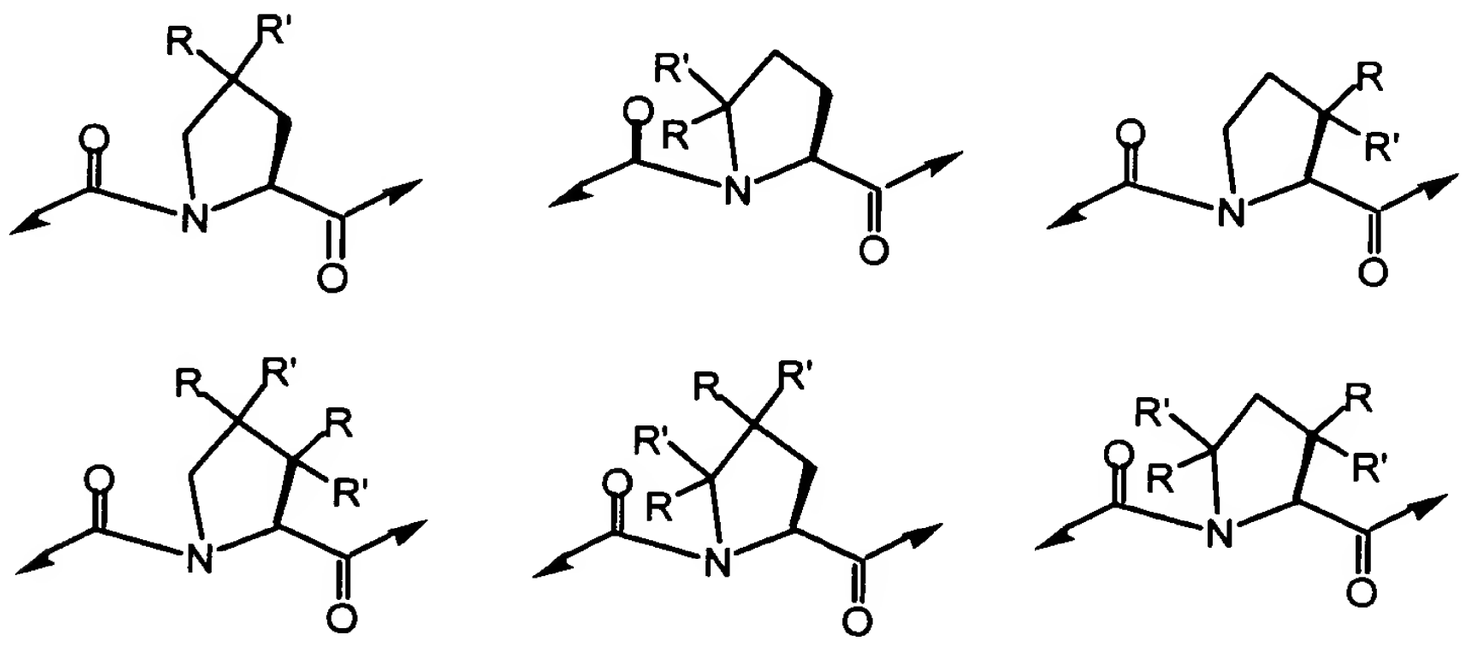


is

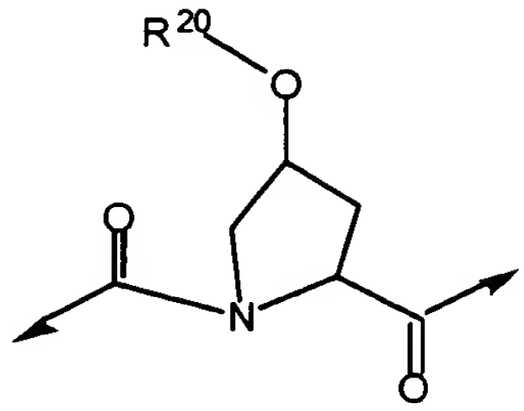


a

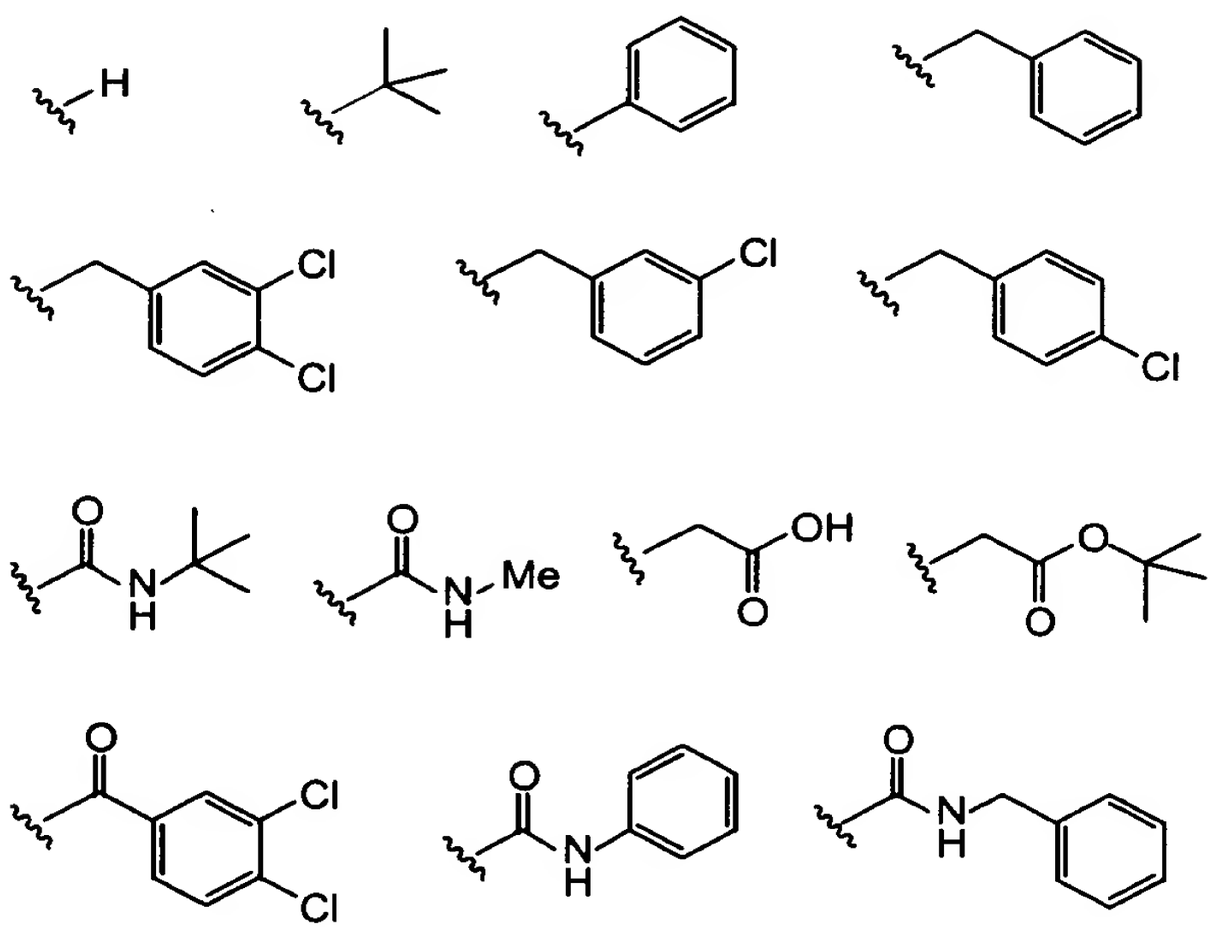
19. The compound of claim 18, wherein structure a is selected from the following structures:



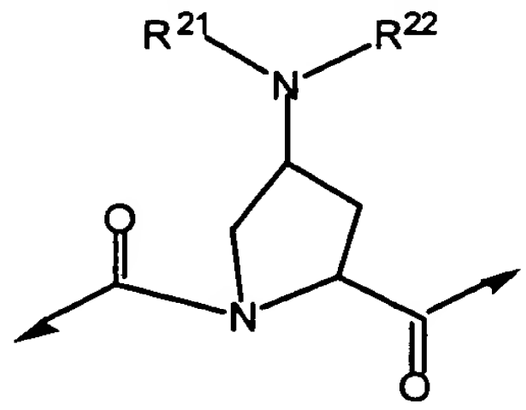
20. The compound of claim 18, wherein structure a is:



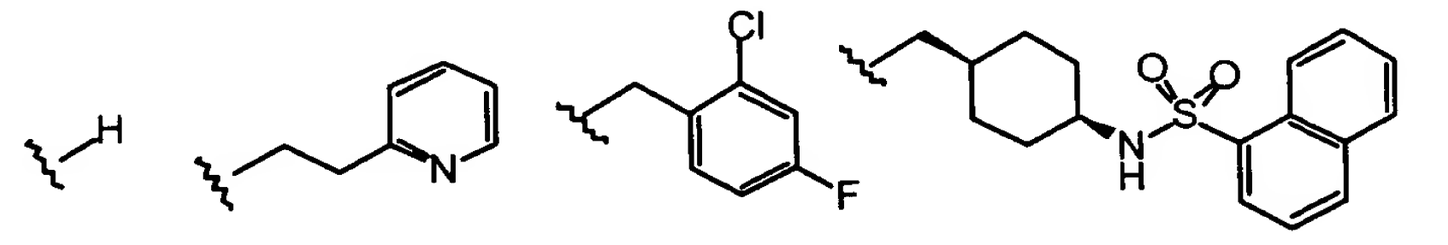
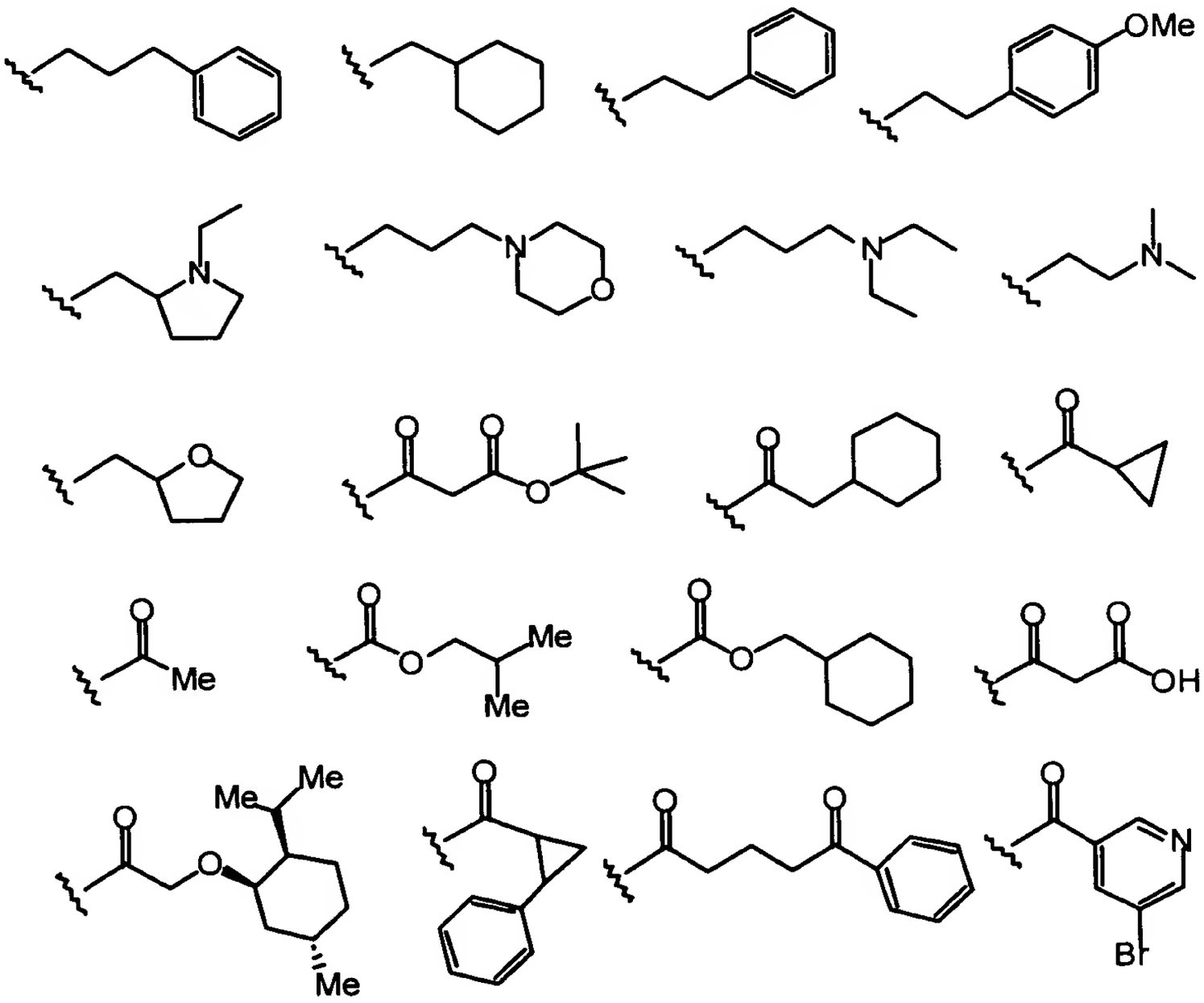
wherein R^{20} is selected from the following structures:



21. The compound of claim 18, wherein structure a is:

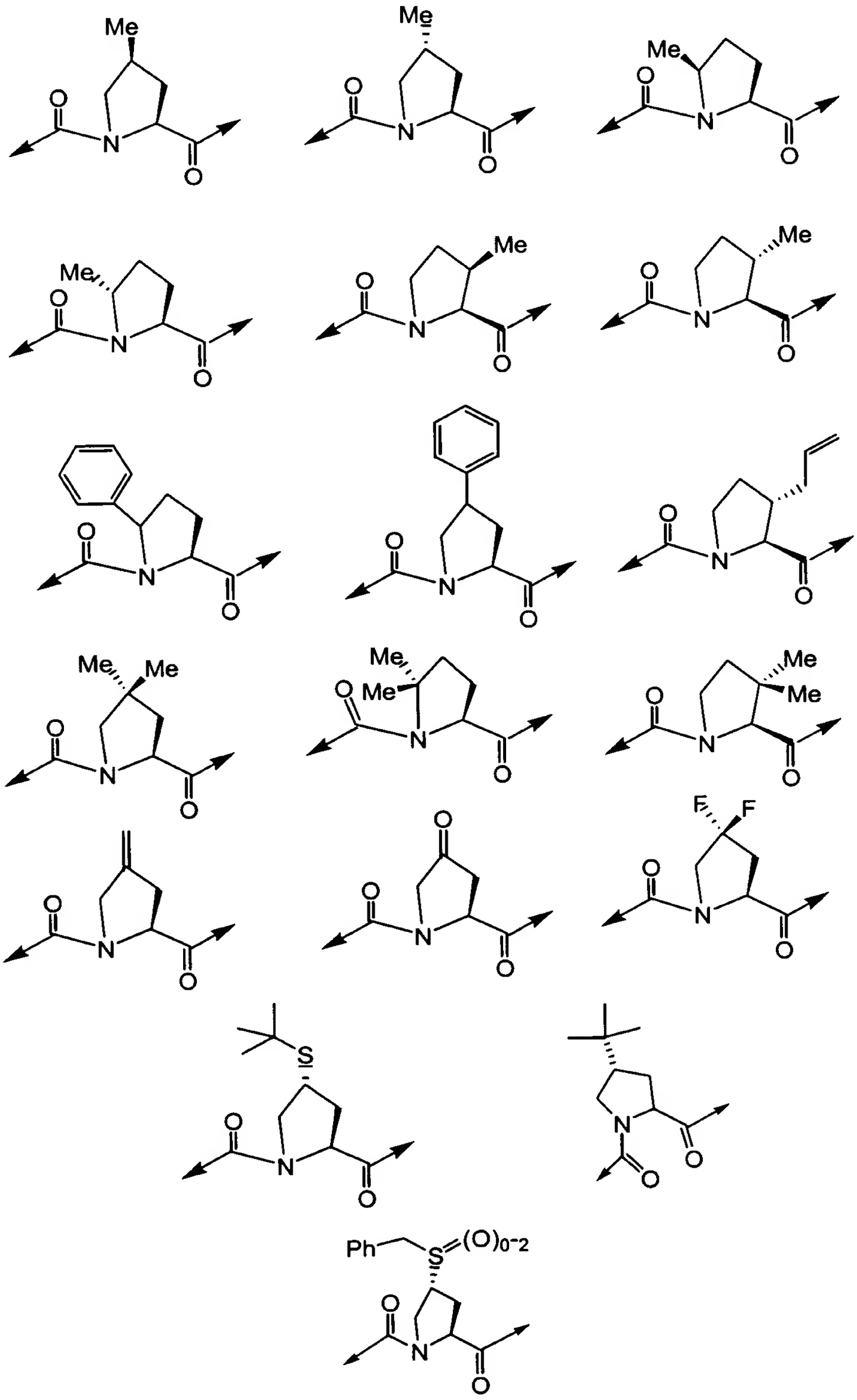


wherein R^{21} and R^{22} may be the same or different and are independently selected from the following structures:

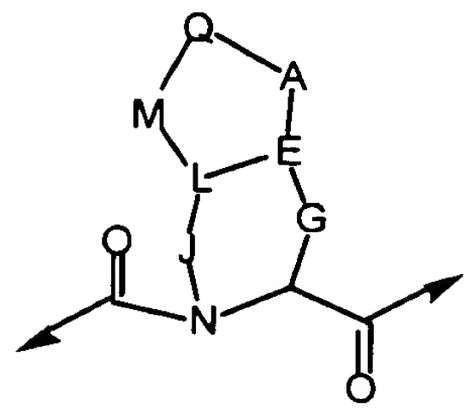



22. The compound of claim 18, wherein structure a is selected from the following structures:

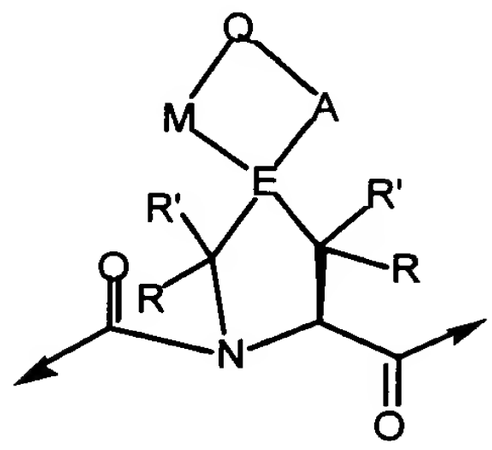
5


Me
O
N
O
Me
O
N
O
Me
O
N
O
Me
O
N
O
Me
O
N
O
Me
O
N
O
Ph
O
N
O
Me
Me
O
N
O
Me
Me
O
N
O
Me
Me
O
N
O
O
N
O
F
F
O
N
O
S
O
N
O
Me
O
N
O
Ph
S
(O)0-2
O
N
O

23. The compound of claim 14, wherein:



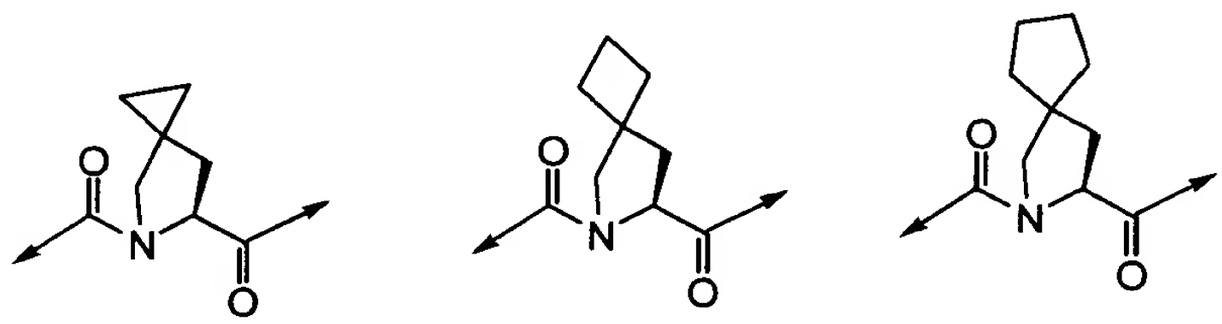
is

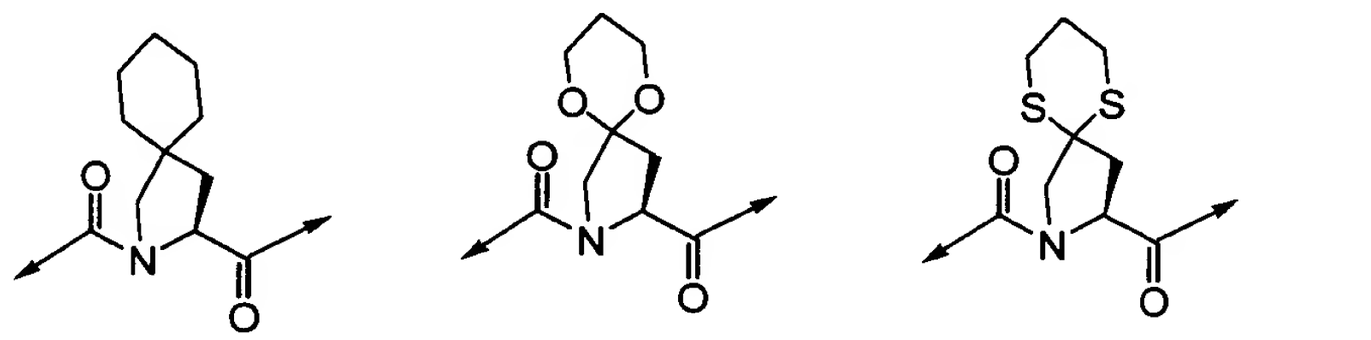


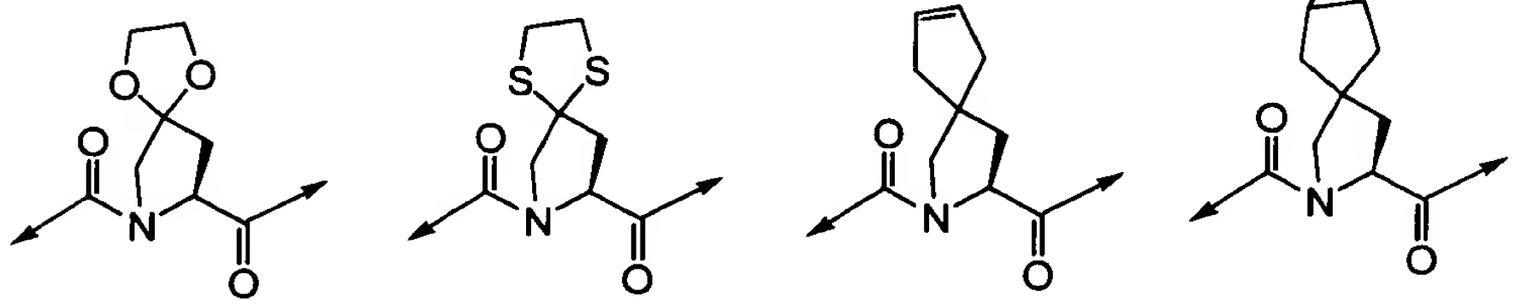
b

wherein Q may be present or absent, and if Q is absent, M is directly linked to A.

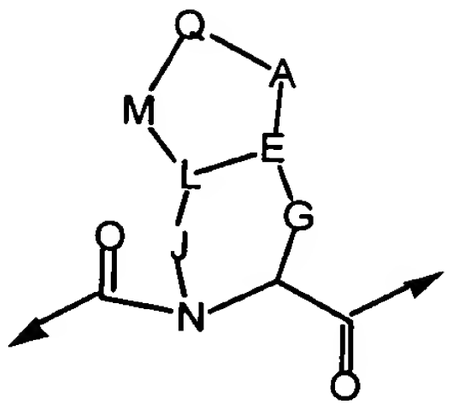
24. The compound of claim 23, wherein structure b is selected from the following structures:



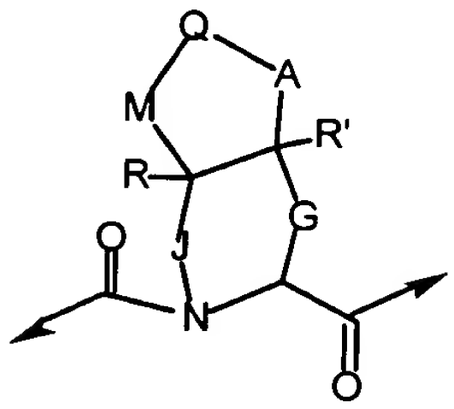




25. The compound of claim 14, wherein:



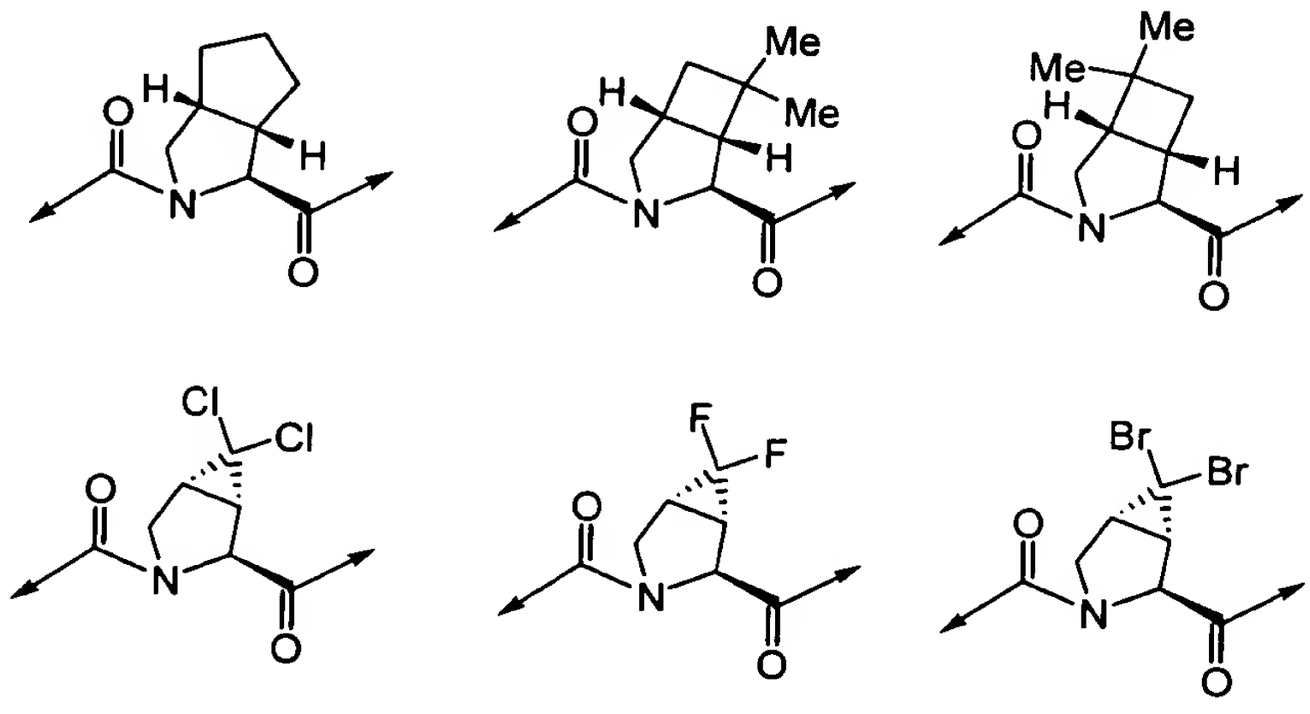
is

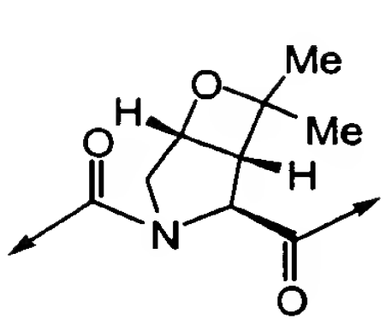


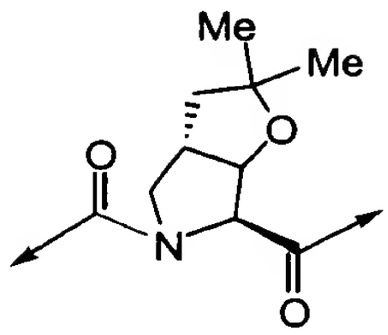
c

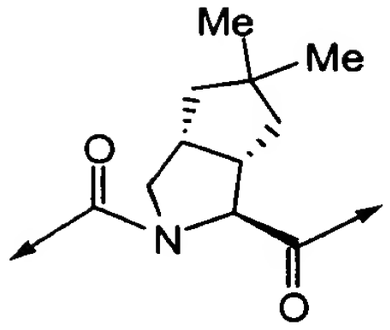
wherein G and J are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; A and M are independently selected from the group consisting of O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; and Q is CH_2, CHR, CRR', NH, NR, O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, and $(CRR')_p$.

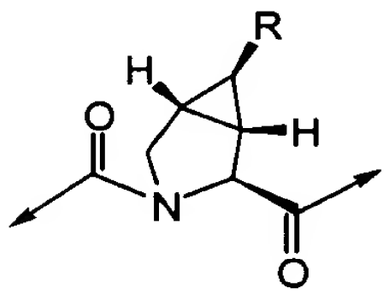
26. The compound of claim 25, wherein structure c is selected from the following structures:

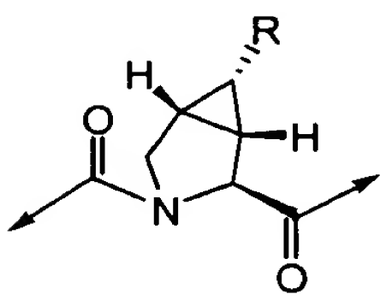


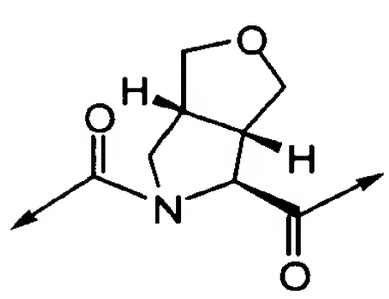

Me
O
H
Me
H
O
N
O

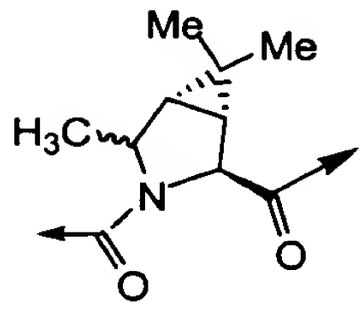

Me
Me
O
O
N
O

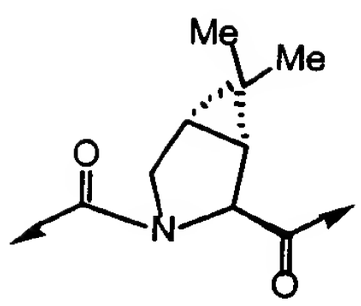
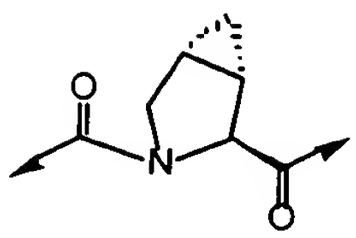
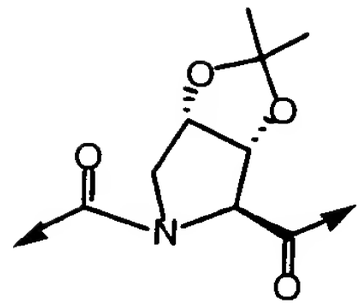
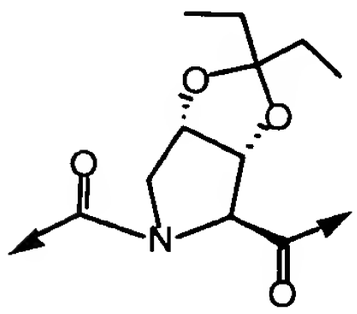
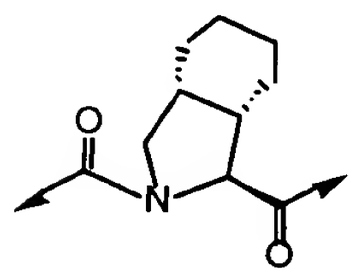
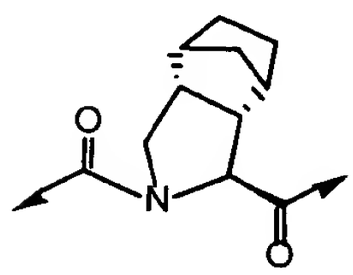
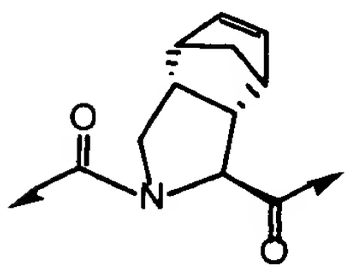
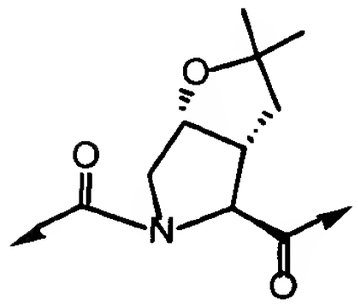
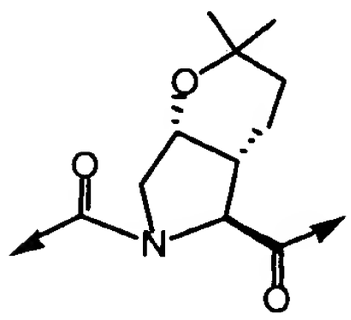
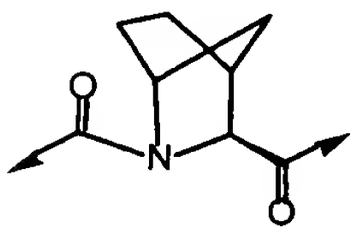
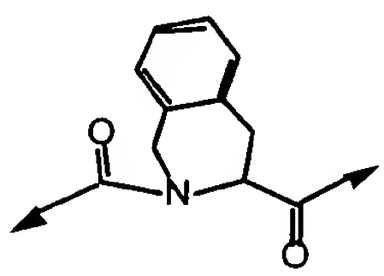
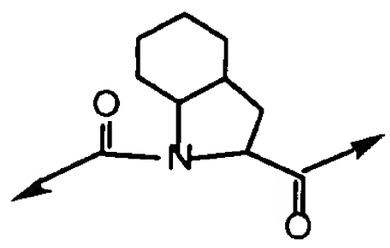
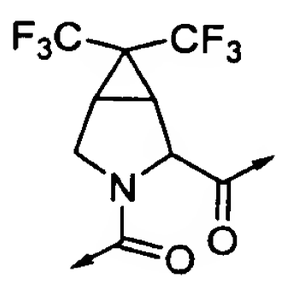

Me
Me
O
N
O


R
H
O
H
N
O

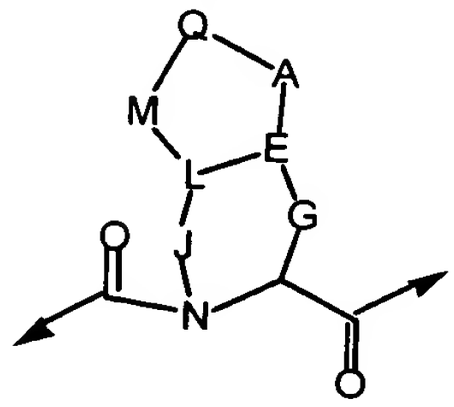

R
H
O
H
N
O


O
H
O
H
N
O

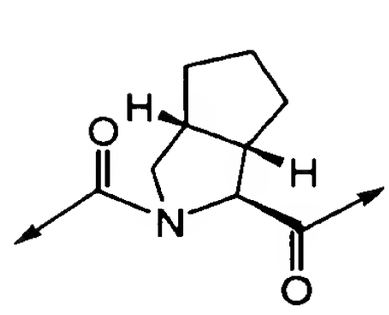
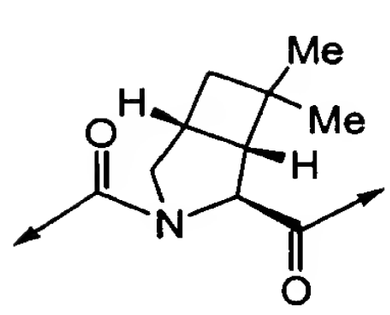
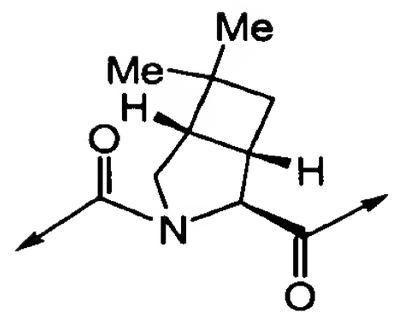
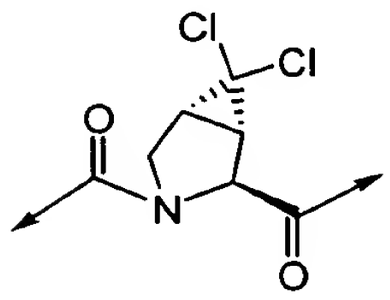
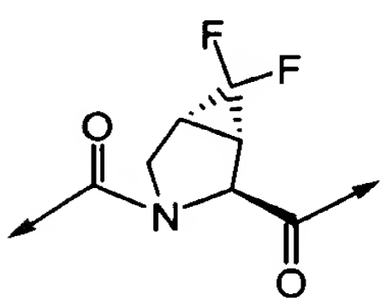
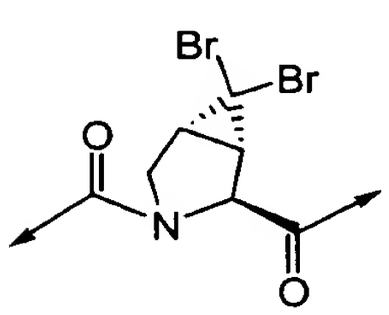
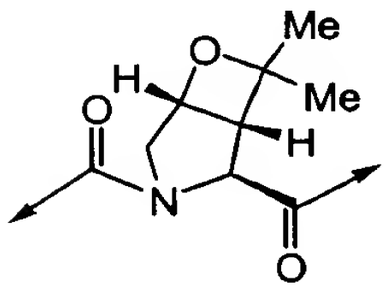
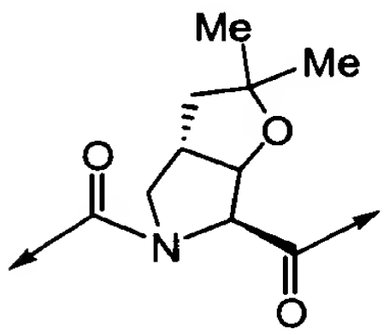
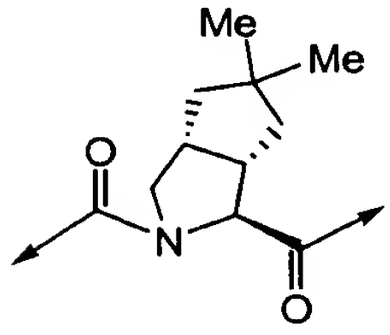
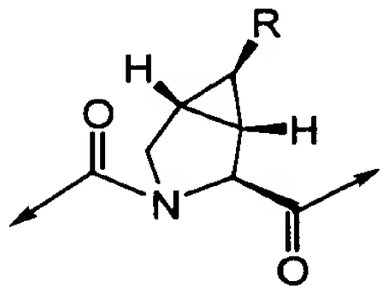
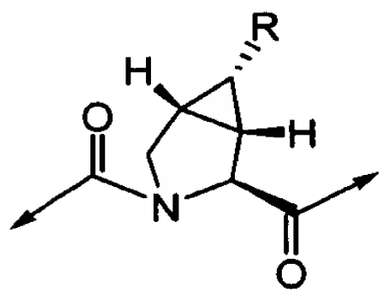
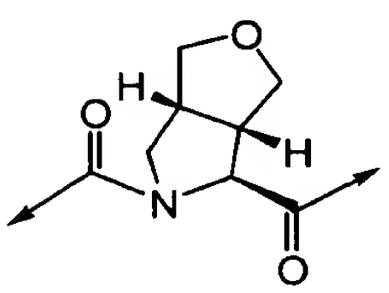
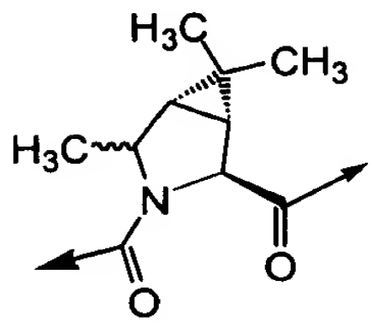

Me
Me
H3C
N
O
O

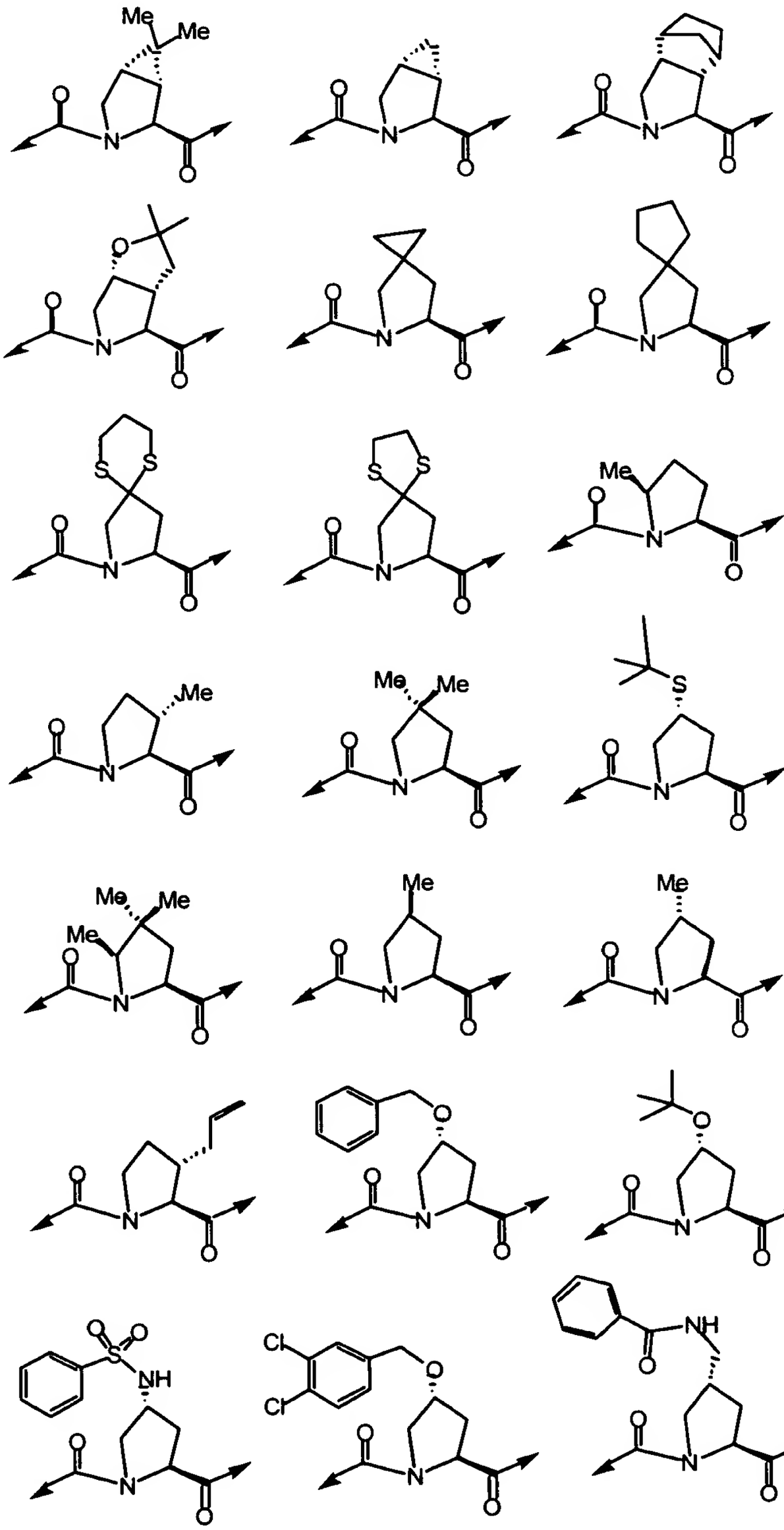














27. The compound of claim 14, wherein:

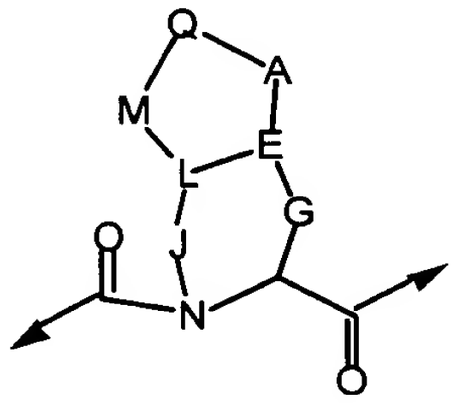


is selected from the following structures:

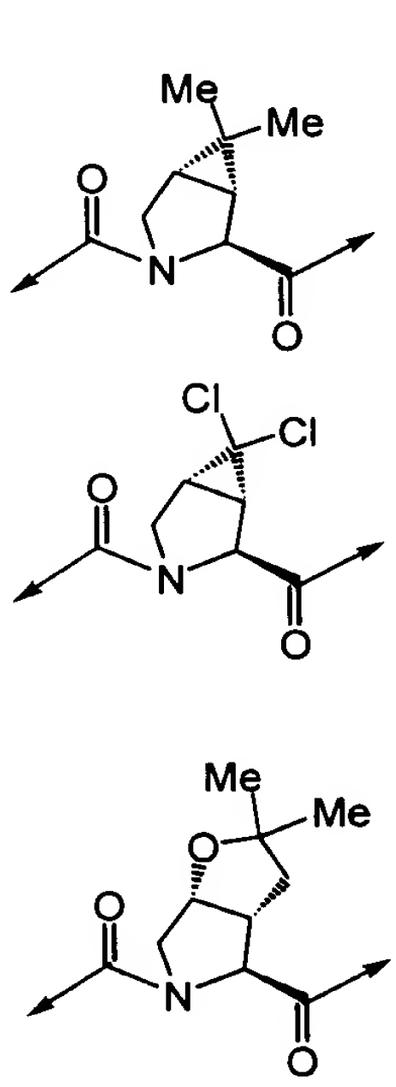
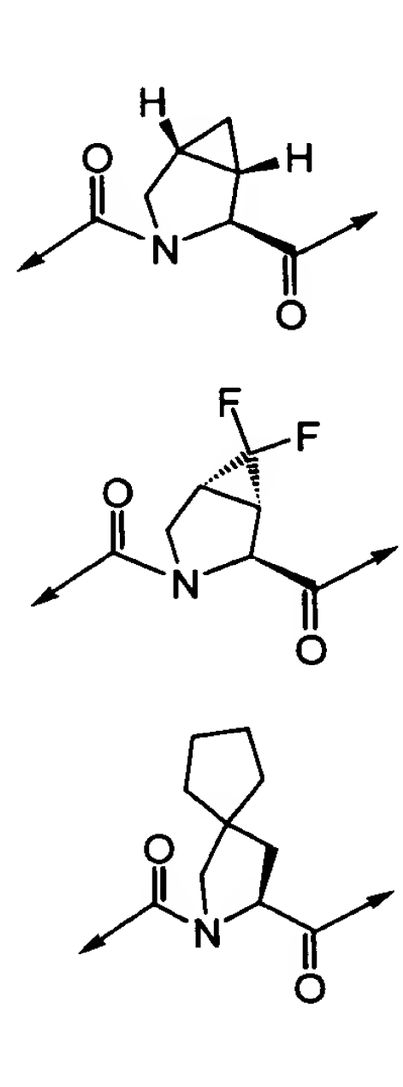
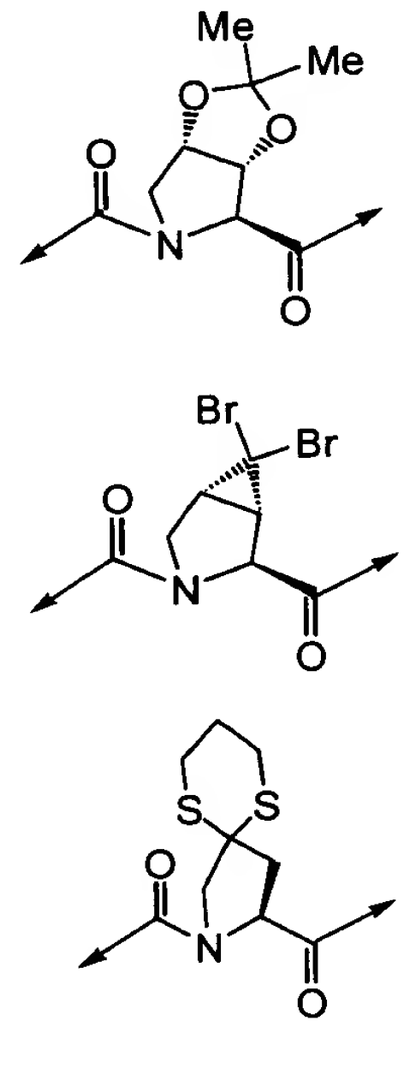














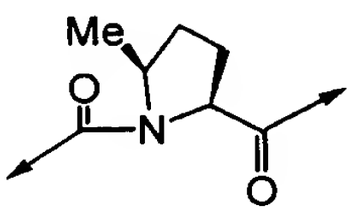
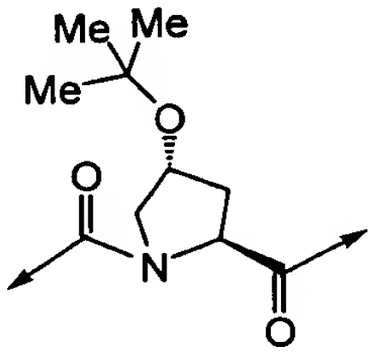
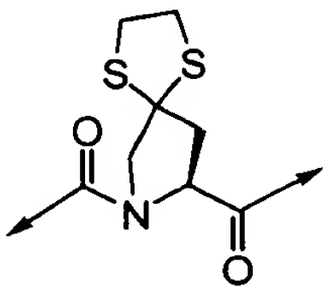
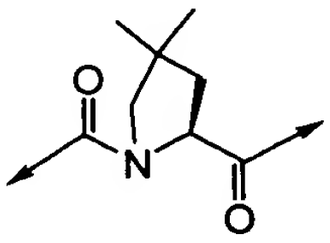
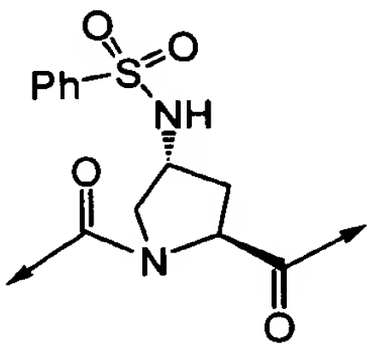
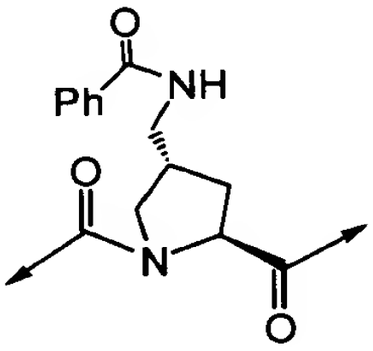


28. The compound of claim 27, wherein:



is selected from the following structures:

29. A pharmaceutical composition comprising as an active ingredient a compound of claim 1.

30. The pharmaceutical composition of claim 29 for use in treating disorders associated with HCV.

31. The pharmaceutical composition of claim 29 additionally comprising a pharmaceutically acceptable carrier.

32. The pharmaceutical composition of claim 31, additionally containing an antiviral agent.

33. The pharmaceutical composition of claim 32, still additionally containing an interferon.

34. The pharmaceutical composition of claim 33, wherein said antiviral agent is ribavirin and said interferon is α-interferon or pegylated interferon.

35. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of a compound of claim 1.

36. The method of claim 35, wherein said administration is oral or subcutaneous.

37. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV.

38. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate contact a compound of claim 1 and a pharmaceutically acceptable carrier.

39. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers, rotamers, tautomers, racemates and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being selected from the compounds of structures listed below: